

# **Advances in Postoperative Pain Management**

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**Doctor of Medicine**

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**By**

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**University of Leicester**

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## Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
COX	Cyclooxygenase
eg	for example
EPIC	Electronic Patient Information Controller
h	hours
iv	Intravenous
im	Intramuscular
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds Ratio
PCA	Patient Controlled Analgesia
PONV	Postoperative nausea and vomiting
RCT	Randomised Controlled Trial
SD	Standard deviation
TAH	Total Abdominal Hysterectomy
VAS	Visual Analogue Scale
y	Years

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## **Statement of collaboration**

The investigations described in this thesis were performed in collaboration with the colleagues who appeared as authors in the publications listed in Chapter 7.

However, I personally undertook all the studies. The process involved consenting patients, liaising with anaesthetic and surgical colleagues, preparing the data collection booklets and collecting the data. I analysed the data, wrote the first draft of the investigations, presented the results to the Anaesthetic Research Society and was the person who prepared the manuscripts for publication in peer-reviewed journals.

## Summary

Until recently, pain relief after all but minor surgery was managed usually by intermittent intramuscular administration of opioids. This method of analgesia did not provide satisfactory pain relief especially after major surgery as it produced marked fluctuation in the plasma concentration of opioid and therefore fluctuation in pain relief. This method has been superseded by intravenous opioids from Patient Controlled Analgesic devices, and also by epidural infusions of opioids with local anaesthetics. Over the past 10 years, introduction of these advanced methods of analgesia has coincided with the evolution of acute pain services in the UK.

Despite these improvements, management of postoperative pain still depends on administration of opioids that are associated with sedation, respiratory depression, gastrointestinal ileus, nausea and vomiting. These adverse effects delay recovery and rehabilitation after surgery. Currently, there is no available replacement for opioids.

The adverse effects associated with opioid administration are related partly to the dose administered. Thus, addition of other analgesic techniques that minimise opioid consumption are potentially useful. This “multi-modal” approach may lead to improvements not only in the quality of analgesia but also in convalescence after surgery.

Local anaesthetics and NSAIDs are two important groups of analgesics which are not associated with the adverse effects of opioids. However, on their own, they do not provide sufficient analgesia for most surgical procedures. Consequently they may be

used as adjuvants with opioids for analgesia after major surgery; this has the advantage of reduced requirement for morphine in comparison with the dose of opioid when used as the sole analgesia.

This thesis describes studies designed to reduce the dosage of morphine for postoperative analgesia and an assessment of potential benefits in terms of reduction in side effects. Five prospective double blind randomised placebo controlled clinical trials have been undertaken: three on the administration of local anaesthetics, and two on NSAIDs. Two models of surgery have been used for investigations. As an example of an invasive standardised surgical procedure associated with severe postoperative pain, I have studied patients undergoing total abdominal hysterectomy (TAH) via a Pfannenstiel incision. I also studied patients undergoing laparoscopy as an example of a minimally invasive technique that has become established in surgical practice over the past decade and is associated with moderate postoperative pain.

In patients who had TAH, I found that a combination of intraperitoneal and incisional bupivacaine with epinephrine was associated with significant morphine sparing analgesia for 4 h postoperatively. Patients experienced significantly less pain on movement with this technique compared with placebo. However, there were no significant differences in PONV and sedation between the two treatment groups.

Intraperitoneal local anaesthetics appeared to have a modest analgesic effect after laparoscopic cholecystectomy. Intraperitoneal administration of levobupivacaine with epinephrine was associated with significantly lower total abdominal pain on inspiration, compared with placebo. However, I was not able to demonstrate

significant differences in rescue morphine consumption, PONV or sedation, between the two treatment groups.

I also studied the administration of local anaesthetics via the transcervical route during laparoscopic sterilisation with Filshie clips. These clips are believed to cause pain of a spasmodic nature and I compared the analgesic effects of bupivacaine, papaverine and normal saline. Unfortunately, there were no significant differences between the three treatment groups in pain, rescue analgesic consumption or PONV.

In addition to local anaesthetics, I also examined how NSAIDs may be useful for postoperative analgesia. After TAH, rectal diclofenac, a non-selective NSAID, was found to reduce morphine consumption, improve postoperative analgesia and was associated with reduced adverse effects such as sedation and nausea.

Another class of NSAIDs, termed COX-2 inhibitors, has become available recently and these are thought to be of great potential use because of a reduction in some side effects compared with non-selective NSAIDs. I studied the analgesic effects of iv parecoxib after TAH and found that it was associated with significant reductions in morphine consumption and pain scores on sitting, compared with placebo.

In summary, the results of the investigations described in this thesis show that local anaesthetics and NSAIDs are useful as analgesic adjuncts after major and minimally invasive surgery; in several studies, they are associated with improved pain relief, a reduction in opioid requirement and a reduction in undesirable side effects such as nausea and sedation.

# Chapter 1

## Part 1: Background

### Current methods of managing postoperative analgesia.

#### 1.1. Introduction

Moderate or severe postoperative pain is associated patient dissatisfaction (Myles 2000). High quality pain relief after surgery and anaesthesia is necessary to improve patient satisfaction, facilitate recovery and minimise suffering. Provision of analgesia may be considered at various levels, from the national and hospital perspective of commissioning acute pain services to the specific method of analgesia delivered to an individual patient.

Before the 1990s, the majority of hospitals in the UK had no formal provision for managing pain after surgery. In 1990, 2.8 % of hospitals in the United Kingdom had an acute pain service compared with 42% (Windsor 1997), 57% (Audit Commission) and 92% (Austin 2002) in 1994, 1997 and 2002, respectively.

The impetus for change appeared to originate from publication of a landmark document in 1990 by the Working Party on pain after surgery of the Royal College of Surgeons of England and the College of Anaesthetists (Commission on the Provision

of Surgical Services 1990). It recommended improved education of staff, assessment of pain, more effective use of existing methods of analgesia and the introduction of new techniques. Other publications from Wales, Scotland and North America have reiterated the importance of providing high quality postoperative pain relief (NHS Wales 1997, Scottish Office 1996, ASA 1995).

The type of analgesia provided to individual patients should be tailored to the pain that is anticipated from surgery. Simplistically, methods of analgesia may be broadly classified into:

- administration of simple analgesics such as NSAIDs, often used in addition to skin infiltration or regional blocks eg inguinal nerve block;
- administration of intramuscular opioids with or without local anaesthetic blocks;
- administration of advanced techniques ie epidural infusions (Wheatley 2001) and iv opioids by PCA (Macintyre 2001).

The role of an Acute Pain Service is to provide formal advice on pain relief after surgery and also to supervise advanced methods of analgesia. In current anaesthetic practice, patients undergoing major surgery eg TAH receive one of these two advanced methods of analgesia. For more minor surgery eg laparoscopic cholecystectomy and laparoscopic sterilisation, patients are intermittently given strong opioids such as morphine in addition to simple analgesics.

Despite considerable improvements in analgesic provision, the major issue in dealing with postoperative pain is how to achieve complete patient comfort and rapid ambulation after surgery. The use of opioids by intramuscular injection or PCA is not ideal; it is associated with adverse effects such as PONV, sedation and respiratory depression. These factors have been shown to be associated with delayed discharge from hospital (Pavlin 1998).

The purpose of this thesis is to examine ways in which some of the disadvantages of opioid analgesia may be obviated. In the following sections, I shall discuss the background to methods that may be used to minimise the dose of systemic opioids, ie local anaesthetics and NSAIDs. In addition, I shall review one of the major problems of opioid analgesia ie PONV and how it may be managed.

## **1.2. Postoperative analgesic provision and outcome**

The introduction of Acute Pain Services appeared initially to be associated with reductions in patients' pain intensity after surgery (Gould 1992). However, in a recent review of 410 publications of pain relief after major non-cardiac surgery, the over all incidence of moderate to severe pain was 30% and that of severe pain was 11% (Dolin 2002). These figures are consistent with a recent investigation by the Clinical Standards Advisory Group who showed that 17% of patients in 12 representative NHS hospitals reported severe pain after surgery (CSAG 1999). Reduction of pain intensity is important, but an additional important question to consider is whether the quality of analgesia can improve outcome after surgery. However, in a recent review of 44 audits and 4 clinical trials referenced in Medline from 1966 to 2002, there was little evidence that acute pain services have improved postoperative outcome (Werner 2002).

Postoperative outcome is determined by surgical expertise, patient comorbidity and anaesthetic care, and is thus unlikely to be influenced by a single factor such as postoperative analgesia. Acute pain services represent a framework for delivery of pain relief and they comprise several components involving a multidisciplinary team that provides variable levels of service. The CSAG has shown recently that 24% of patients were sent home without analgesia and 29% of patients reported that no advice was given on pain relief treatments (CSAG 1999). There have been difficulties in commissioning and planning local acute pain services that have been attributable to the lack of formal consideration of how pain services should be developed by purchasers and providers (CSAG 1999).

The failure of acute pain services to demonstrate improvements in postoperative outcome may be due not only to inadequate analgesia but also to adverse effects of opioid analgesia and epidural analgesia. The ideal analgesic method should be non-invasive and simple to administer and patients should experience strong long lasting pain relief without any adverse effects such as sedation, PONV and delayed return of gastrointestinal motility. It is clear that further measures are needed if improvements in analgesic outcomes are to occur (McHugh 2002).

### **1.3. Methods used to minimise use of systemic opioids**

In this section, I shall focus on methods to minimise use of systemic opioids. They include administration of local anaesthetic agents into the peritoneal cavity and also into epidural and spinal space. In addition, NSAIDs are often used in the perioperative period and I shall describe beneficial outcomes as well as problems associated with them.

#### **1.3.1. Local anaesthetics to minimise use of opioids**

In this section, the physical properties, toxicity and clinical effects of local anaesthetics are discussed in addition to their administration via the intraperitoneal, epidural and spinal routes.

#### **Physical properties**

The local anaesthetics administered to patients enrolled in the investigations presented in this thesis were bupivacaine and levobupivacaine. Bupivacaine is classified as an amide local anaesthetic and has a butyl group on its piperidine nitrogen atom. This butyl group distinguishes it from ropivacaine and mepivacaine that have propyl and methyl groups, respectively. Bupivacaine is 95% protein bound and has a molecular weight of 288 and a pKa of 8.1. Its partition coefficient (N heptane/buffer) is 10 and its mean uptake ratio in rat sciatic nerves is 3.3 (McClure 1996).

Bupivacaine exists as a racemic mixture of enantiomers that exhibit optical and stereoisomerism. Optical isomers are dextrorotatory (+) and laevorotatory (-), when they rotate light clockwise and anticlockwise, respectively. These are also termed “R” from the Latin rectus (right) or “S” from the Latin sinister (left), when the spatial arrangement of ligands from largest to smallest, around the chiral centre, is clockwise and anticlockwise, respectively (Burke 2002). Levobupivacaine is the S (-) enantiomer of bupivacaine.

### **Toxicity and clinical effects of local anaesthetics**

Bupivacaine and levobupivacaine have the potential to cause central and cardiovascular toxicity. Despite initial reports of accidental deaths after administration (Albright 1979), bupivacaine has become well established in anaesthetic practice. To minimise the risk of toxicity, there are restrictions on the dose and route of administration: eg in contrast to lidocaine, intravenous administration of bupivacaine is contraindicated.

In recent years, there has been an evaluation of bupivacaine's chirality. Levobupivacaine is now commercially available and is thought to have a better therapeutic index than bupivacaine (Tucker 2000). In sheep, levobupivacaine was less CNS toxic and less likely to cause fatal arrhythmias than bupivacaine (Chang 2000). The mean (SD) convulsive dose of 127 (23) mg of levobupivacaine was greater than that of 69 (12) mg to 85 (11) mg of racemic bupivacaine. In addition, the estimated

mean (SD) fatal dose of 277 (51) mg of levobupivacaine was significantly higher than 156 (31) mg of racemic bupivacaine.

These findings concur with a study in human volunteers in which the effects of intravenous infusions of levobupivacaine and racemic bupivacaine were investigated. The reductions in mean stroke index, acceleration index and ejection fraction after levobupivacaine were significantly lower than those observed after racemic bupivacaine (Bardsley 1998). McLeod has reviewed additional data from two human volunteer studies (McLeod 2001). There was a greater proarrhythmic potential after bupivacaine because it caused significantly greater QTc prolongation than levobupivacaine. There has also been a case report of accidental intravenous administration of levobupivacaine 7.5 mg ml<sup>-1</sup> 19ml after attempted epidural cannulation. There was no cardiovascular toxicity and serum bupivacaine concentrations were 2.7 µg ml<sup>-1</sup> and 1.1 µg ml<sup>-1</sup>, 14 and 120 minutes respectively, after administration (Kopacz 1999). In addition, the only central effect was shouting and writhing; no convulsions were reported.

Although there are major differences in toxicity between racemic bupivacaine and levobupivacaine, their clinical efficacies are equivalent. It has been shown in many studies reviewed by McLeod (McLeod 2001), that both local anaesthetics are associated with similar analgesic effects in patients having brachial plexus blocks, inguinal herniorrhaphy, peribulbar blocks, spinals and epidurals.

### **Intraperitoneal administration of analgesia and outcome**

Data from a nationwide survey in the United Kingdom of anaesthesia for gynaecological laparoscopy revealed that local anaesthetic solutions are administered commonly to incisional sites and into the peritoneal cavity (Simpson 1999). The main advantage of using local anaesthetics is that they do not have the adverse effects of opioids that may delay recovery and discharge from hospital. These adverse effects include postoperative nausea, sedation, impairment of return of gastrointestinal motility and pruritis. In addition, time to return of bowel function in the postoperative period may be reduced when the use of opioids is obviated by administering local anaesthetics (Groudine 1998).

Although NSAIDs provide morphine sparing effects, they do not appear, on their own, to provide sufficiently reliable postoperative analgesia for minimally invasive laparoscopic surgery (Alexander 1997). In addition, they have the disadvantage that they may cause gastric irritation in addition to impairing platelet and renal function. In the perioperative period, many patients are at risk of these problems because of enforced starvation, tissue trauma and dehydration. Additional methods of analgesia are thus necessary.

Local anaesthetics have been administered into the peritoneal cavity during minimally invasive procedures such as laparoscopic cholecystectomy and gynaecological laparoscopy for sterilisation and diagnosis (Moiniche 2000), in addition to open abdominal procedures such as total abdominal hysterectomy (Williamson 1997, Ali 1998). The rationale for this route of administration is that the peritoneum is exposed

to blockade of visceral nociceptive conduction, thereby providing an additional mechanism of analgesia. However, systemic absorption from the large peritoneal surface may also occur and this may be a further mechanism of analgesia.

The hypothesis proposing a systemic effect stems from studies performed using intravenous lidocaine. It has been shown that intravenous lidocaine, 1.5 mg kg<sup>-1</sup> bolus and 2 - 3 mg min<sup>-1</sup> infusion, reduced morphine consumption and total pain scores significantly compared with placebo, following radical retropubic prostatectomy (Groudine 1998). In another clinical trial intravenous lidocaine produced a concentration dependent reduction in pain scores when the plasma concentration exceeded 1.5 µg ml<sup>-1</sup> (Wallace 1996). This systemic mechanism may be explained in part by work on rats in which systemic lidocaine suppressed peripheral ectopic impulse discharge (Devor 1992) and inhibited central excitatory responses to glutamate (Biella 1993).

However, it is uncertain how much a systemic effect bupivacaine has after intraperitoneal administration. The range of mean plasma concentration (0.92 - 1.14 µg ml<sup>-1</sup>) following a standard dose of bupivacaine 100 mg to 150 mg into the peritoneal cavity (Narchi 1992, Raetzell 1995, Scheinin 1995) is well below the toxic concentration of 3 µg ml<sup>-1</sup> (Liu 2001). When unanaesthetised volunteers were given bupivacaine intravenously, systemic concentrations similar to those measured after intraperitoneal administration were associated with neurological symptoms such as paresthesia, tingling and perioral numbness (Knudsen 1997, Scott 1989). However, it remains unclear if these systemic concentrations are associated with measurable postoperative analgesia.

Although laparoscopic cholecystectomy is a minimally invasive procedure, it is associated with intra-abdominal, incisional and shoulder pain postoperatively (Labille 2002). Many clinical trials have been carried out to assess if intraperitoneal instillation of local anaesthetics to the gall bladder bed and right subdiaphragmatic space are associated with an analgesic effect. Of 13 clinical trials included in a systemic review (Moiniche 2000) of intraperitoneal administration of bupivacaine 50 mg to 200 mg, in volumes of 10 ml to 100 ml, significant reduction in over all pain occurred in 7 trials but not in the other six. In addition, supplemental analgesic consumption was reduced significantly in five. This systematic review of bupivacaine concurs with a subsequent clinical trial in which intraperitoneal lidocaine 200 mg in 200 ml instilled under the right diaphragmatic surface increased time to first analgesia from 25 min to 105 min after laparoscopic cholecystectomy (Elhakim, Elkott 2000). Interestingly, in a recent study, intraperitoneal combination of local anaesthetic and a NSAID was shown to be more effective in reducing pain scores and opioid consumption than either placebo or intraperitoneal local anaesthetic with intravenous NSAID. Analgesic effects were greater in patients who had intraperitoneal lidocaine 200 mg with intraperitoneal tenoxicam 20 mg diluted to 200 ml compared with either placebo or intraperitoneal lidocaine 200 mg in 200 ml with intravenous tenoxicam 20 mg (Elhakim, Amine 2000). Thus it would appear that for laparoscopic cholecystectomy, intraperitoneal local anaesthetic solutions produce a modest analgesic effect which may not be adequate for routine analgesia.

Clinical trials of intraperitoneal instillation of local anaesthetics during gynaecological laparoscopy appear to demonstrate more effective analgesia possibly because this

operation is less traumatic than laparoscopic cholecystectomy (Moiniche 2000). In a systematic review of bupivacaine or etidocaine dripped onto the Fallopian tubes during laparoscopic sterilisation under general anaesthesia, pain scores and supplemental analgesic consumption were reduced significantly for up to 2 h postoperatively. Furthermore, intraperitoneal lidocaine, infiltrated into the mesosalpinx or into the fallopian tubes, or coating Filshie clips produced similar analgesic effects (Moiniche 2000). This has been confirmed in awake postpartum patients when intraperitoneal lidocaine 0.5% 80 ml reduced the need for supplemental fentanyl, ketamine and rescue general anaesthesia during tubal ligation (Visalyaputra 1999). In addition, intraperitoneal instillation of ropivacaine 150 mg during gynaecological laparoscopy produced a statistically significant 24 h morphine sparing effect compared with placebo (Goldstein 2000).

The intraperitoneal route appears also to be an effective method of postoperative analgesia following administration of a combination of local anaesthetic and opioid. In a clinical trial of 100 patients undergoing laparoscopic tubal ligation, pain scores at rest and on movement were significantly less in patients who had a combination of intraperitoneal meperidine 50 mg and bupivacaine 0.125% 80 ml with epinephrine 1:200 000 compared with those who had a combination of intramuscular meperidine 50 mg and intraperitoneal bupivacaine 0.125% 80 ml with epinephrine 1: 200 000 (Colbert 2000).

In summary, therefore, it seems that intraperitoneal instillation of local anaesthetics is effective for gynaecological laparoscopy but may not be so for laparoscopic cholecystectomy (Moiniche 2000). Laparoscopic cholecystectomy is a longer

procedure with greater tissue dissection than gynaecological laparoscopy. Recent evidence suggests that instillation of local anaesthetics both into the peritoneum and into the incision may be required following laparoscopic cholecystectomy. Instillation of ropivacaine 286 mg in 66 ml in this way during laparoscopic cholecystectomy, produced lower pain scores and reduced morphine requirements compared with placebo (Bisgaard 1999).

While intraperitoneal local anaesthetics have produced analgesic effects following gynaecological laparoscopy, they have not done so following TAH via a Pfannenstiel incision (Williamson 1997, Ali 1998). Intraperitoneal instillation of either bupivacaine 0.5% 20 ml with epinephrine 1:200 000 diluted to 50 ml with normal saline, or lidocaine 2% 20 ml with epinephrine 1:200 000 diluted to 50 ml with normal saline, did not demonstrate any opioid sparing effects compared with placebo (Ali 1998). It is likely that while intraperitoneal local anaesthetics may block visceral nociceptive conduction following minimally invasive surgery such as gynaecological laparoscopy, they do not block afferent nociceptive transmission from cutaneous sites. We postulated that the opioid sparing effects of intraperitoneal local anaesthetics are very mild and are overwhelmed by major surgery.

The difference in outcome of studies on intraperitoneal instillation of local anaesthetics may be due to the type of surgery and the location, dose and timing of instillation. The failure in some studies to show an analgesic effect may result from rapid dilution of local anaesthetic in the peritoneal cavity (Schulte-Steinbery 1995). It is not possible, however, to increase the dose of local anaesthetic without increasing the risk of systemic toxicity. Although potentially more toxic than lidocaine,

bupivacaine has the advantage that it has a longer duration of action. However, in clinical trials, it has been found that the analgesic effects of bupivacaine have been short-lived. It has been shown in a mouse model that intraperitoneal bupivacaine in a liposomal formulation may prolong the duration of action and also reduce the possibility of systemic toxicity (Grant 1994). An alternative is levobupivacaine, the *s* (-) enantiomer of bupivacaine, that is thought to have similar analgesic effects and duration as racemic bupivacaine but with a reduced risk of systemic toxicity (Foster 2000), thus allowing the possibility of administration of a larger and more potent dose.

## **Administration of local anaesthetics by the epidural and spinal route**

Perioperative administration of local anaesthetics by the epidural (and possibly spinal) route requires attention because it has had a major impact on outcome after surgery. This method leads to attenuations in the endocrine-metabolic responses that occur postoperatively. In this section, I will review outcome after surgery associated with administration of local anaesthetics by the epidural route. Gastrointestinal outcome is described in a separate section below.

### *Effect of epidural and spinal local anaesthetics $\pm$ opioids on outcome after surgery*

Administration of local anaesthetics in combination with an opioid into the epidural space appears to be effective for postoperative analgesia. In a qualitative review by Wheatley of RCTs comparing combinations of epidural bupivacaine and an opioid with intravenous PCA morphine, it was shown that the local anaesthetic technique provided better dynamic pain relief than systemic morphine (Wheatley 2001).

From a review of 141 clinical studies up to 1997, it was shown that epidural and spinal anaesthesia are associated with significant improvements in morbidity and mortality after non-cardiac surgery (Rodgers 2000). The odds reduction (SE) for postoperative mortality within 30 days, deep vein thrombosis, pulmonary embolism, perioperative transfusion > 2 units, postoperative bleeding requiring transfusion, pneumonia and respiratory depression was 30(11)%, 44(10)%, 55(15)%, 50(10)%,

55(15)%, 39(9)% and 59(19)%, respectively. Although these results seem favourable, it remains unclear whether they are a direct effect of neural axial blockade or the avoidance of general anaesthesia. On closer inspection, it may be seen that improvements in outcome occurred in patients who had orthopaedic surgery. Thus, the interpretation that reduction in mortality is independent of surgical subgroup is likely to be incorrect and should be applicable only to orthopaedic patients.

These findings appear to be consistent with those of Kehlet who reviewed RCTs comparing epidural local anaesthetics with and without opioids to systemic opioid analgesia (Kehlet 2001). Complications described in each RCT were summed rather than subjected to a formal meta-analysis. From the data presented, it can be seen that the incidence of pulmonary complications ie pneumonia or reintubation, and of thromboembolism after major abdominal surgery was significantly lower in patients receiving epidural analgesia compared with systemic opioid analgesia. In addition, there was a trend to improved cardiac morbidity ie heart failure, ischaemic events and arrhythmias in patients who had epidurals compared with those who had systemic opioids.

Subsequently, Park has shown in a RCT that myocardial infarction in addition to respiratory failure and stroke were reduced in patients receiving local anaesthetics via epidurals for aortic surgery (Park 2001). However, in patients having other types of abdominal surgery, epidural analgesia did not appear to improve outcome (Park 2001). The over all results from the study by Park did not demonstrate a treatment effect of epidural local anaesthetics and they are consistent with the negative findings of the retrospective analysis of data collected in a prospective multicentre Australian

RCT (Peyton 2003). It is possible that the failure to demonstrate a convincing treatment effect may be, in part, attributable to the method of epidural analgesia. For prevention of perioperative cardiovascular events and hence possible mortality, a high epidural block appears to be required (Beattie 2001). In the study by Park, we are uncertain of the ratio of thoracic to lumbar catheters, if local anaesthetics were used for all epidurals, and if a sensory block was well established for the whole intraoperative period and for at least 72 h postoperatively. At the time that the studies by Park and Peyton were conceived,  $\beta$  blockers were not administered commonly in the perioperative period. Unfortunately, details of these factors were not available for assessment.

*Comparison of administration of epidural local anaesthetics  $\pm$  opioids with systemic opioid analgesia on gastrointestinal outcome*

**Gastrointestinal motility**

In the postoperative period, local anaesthetics administered by the epidural route appear to have a beneficial effect on gastrointestinal motility compared with systemic opioids (Kehlet 2001). In a review of 16 studies of which 10 were RCTs, it has been clearly demonstrated that return of gastrointestinal motility occurred earlier in patients who had epidural analgesia compared with systemic opioids (Steinbrook 1998). In these studies a variety of end points were used such as time to first bowel sounds, time to first passing of flatus or faeces, transit time of radio-opaque markers and barium transit time. In addition, in three RCTs, it was found that return of gastrointestinal motility was delayed in patients receiving thoracic epidural morphine compared with those receiving thoracic epidural bupivacaine for postoperative analgesia (Steinbrook 1998). It is believed that the effectiveness of thoracic epidurals is due to blockade of inhibitory thoracolumbar sympathetic efferents, allowing unopposed parasympathetic activity via craniosacral efferents. In addition, there is blockade of nociceptive afferent neural impulses, decreased endogenous circulating catecholamines and reduction in the administration of opioids. Despite some lack of evidence for efficacy in postoperative ileus (Neudecker 1999), it is currently believed that epidural analgesia should be used as part of a multimodal care pathway of early nutrition, early mobilisation (Brodner 2001) and minimally invasive surgery that facilitates postoperative recovery and minimises morbidity and duration of hospital stay (Basse 2000).

### Anastomotic leakage

Anastomotic leakage is a serious complication after colorectal surgery. Although the aetiology of this problem includes patient factors such as anaemia and co-morbidity, as well as surgical factors such as bowel preparation and operative expertise, the key clinical question for the anaesthetist is whether there is a relationship between the method of postoperative analgesia and the development of anastomotic leakage.

It has been speculated previously that epidural analgesia would be likely to increase the risk of anastomotic leakage following colorectal surgery because of increased intestinal motility and intraluminal pressure, in addition to possible reduced anastomotic blood supply. This issue has been examined in a review of RCTs available on Medline from 1966 to 2000 (Holte 2001). In 11 RCTs of this review, epidural local anaesthetic with and without opioids was compared with systemic opioids. Although the incidence of anastomotic leakage was 16/255 for epidurals compared with 9/252 for systemic opioids, there was no statistical difference. In addition, data from three RCTs of this review comparing administration of epidural opioid, epidural local anaesthetic and a mixture of epidural opioid and local anaesthetic did not demonstrate a significant difference in risk of anastomotic leakage.

### **1.3.2. Use of NSAIDs to minimise dosage of opioids**

The background to NSAIDs ie their mechanism of action, classification and considerations for use in the perioperative period are discussed in this section.

#### **Mechanism of Action**

Prostaglandins are involved in important physiological functions such as inflammation, platelet function, gastric mucosal integrity and renal blood flow. They are formed from arachidonic acid by the action of membrane-associated COX enzymes, COX-1 and COX-2. Their formation is inhibited in two principal ways (Hawkey 1999):

- *Non-selective inhibition*

This occurs by binding of non-selective NSAIDs at the arginine 120 site of their narrow channel. Binding is instantaneous and occurs by hydrogen bonding.

- *Selective inhibition*

This occurs by binding of selective COX-2 drugs at position 523 where valine is present. In the COX-1 enzyme, the presence of isoleucine at position 523 blocks access and hence inhibition.

## Classification

The currently available drugs may be classified into three groups:

- Non-selective NSAIDs. The COX 2/COX 1 ratio for ibuprofen and naproxen are 2.0 to 6.1 and 0.4 to 9.5, respectively (Furst 1999).
- COX-2 preferential inhibitors eg meloxicam. Meloxicam is 3-77 times more selective for COX-2 than COX-1 and its COX 2 to COX 1 ratio is approximately 0.08. It appears that when the dose of meloxicam is increased from 7.5 mg to 15 mg, there is a reduction in COX-2 selectivity.
- COX-2 selective inhibitors eg celecoxib, rofecoxib, valdecoxib and parecoxib. This group of COX inhibitors do not inhibit COX-1 over the range of doses used clinically. COX 2 to COX 1 ratio for celecoxib, for instance, is 0.007 (Furst 1999).

## **Non-selective NSAIDs in the perioperative period**

### *Analgesic outcomes*

Non-selective NSAIDs have been shown to be useful analgesic adjuncts after major surgery. In many RCTs, investigators have assessed their utility in terms of opioid consumption as well as other outcome measures such as sedation, PONV, time to first flatus and discharge from hospital. As my investigations of NSAIDs were in patients having TAH, I shall review the literature with particular attention to their administration during abdominal surgery.

After abdominal hysterectomy, Parker reported that ketorolac 30 mg at 6 hourly intervals reduced significantly morphine or pethidine PCA consumption as well as time to first flatus (Parker 1994). However, pain intensity, sedation, ambulation and discharge times were not improved by ketorolac. In a review of several other RCTs, Gillis showed that ketorolac is opioid sparing not only after abdominal hysterectomy but also after hip and knee surgery, as well as thoracic surgery (Gillis 1997).

In addition, diclofenac appears to be useful after TAH. Scott showed that rectal diclofenac 100 mg reduced significantly, morphine consumption at 4 hourly intervals in the postoperative period, compared with placebo (Scott 1997). Although, there was also a significant decrease in pain intensity in patients who received diclofenac, no difference in PONV was demonstrated between the two treatment groups. When rectal diclofenac 50 mg was administered on wound closure and at 8 and 16 h after TAH in another RCT, mean (SD) 24 h morphine consumption of 54.9(28.3) mg in the

placebo group was reduced by 40%, to 32.7(27.4) mg (Cobby 1999). However, no significant difference in pain intensity, sedation or PONV was detected.

These findings are confirmed by Luthman in a RCT of patients who had a Caesarean section under spinal anaesthesia (Luthman 1994). Rectal diclofenac 100 mg was associated with a significant morphine sparing effect over a 20 h period postoperatively. Unfortunately, no reduction in sedation or PONV was reported in the diclofenac group compared with placebo.

In another study of patients having TAH, a combination of rectal diclofenac 100 mg and paracetamol 1.5 g, was associated with a significant reduction opioid consumption compared with the individual drugs (Montgomery 1996). The addition of diclofenac appeared to reduce mean (95% CI) 24 h morphine consumption to 27.1(18.5 to 35.8) mg; in comparison mean (95% CI) 24 h morphine administered was 44.9(36.1 to 53.6) mg in patients who had paracetamol alone. Despite this improvement, no significant difference in pain intensity scores, PONV or sedation was described.

In other RCTs, investigators have been less successful in showing analgesic benefits after TAH. For instance, tenoxicam 20 mg or 40 mg iv was not associated with reduced postoperative PCA fentanyl consumption, pain intensity or nausea (Danou 2000). These results are not dissimilar to those described by Thompson who was not able to demonstrate a morphine sparing effect of rectal meloxicam 15 mg (Thompson 2000). However, in this RCT, meloxicam was associated with a significant reduction in pain intensity compared with placebo.

There have been other clinical trials of administration of NSAIDs in combination with paracetamol in the perioperative period. In 4 out of 9 RCTs in a qualitative review, pain scores and rescue analgesic requirements in patients who received a combination of a NSAID and paracetamol were reduced significantly compared with those who were prescribed paracetamol only (Romsing 2002). In another qualitative review of RCTs, NSAIDs were thought to be more effective for analgesia than paracetamol after minor but not major surgery (Hyllested 2002).

In conclusion, it can be seen that NSAIDs are effective analgesic adjuncts because they are likely to reduce postoperative opioid consumption as well as pain intensity. There is some evidence that NSAIDs may be useful when administered in combination with paracetamol, in the perioperative period. However, in many instances, they do not appear to differ from placebo with regard to other outcome measures eg sedation and PONV.

### *Complications of NSAIDs*

Adverse events associated with NSAIDs are principally, haematological, gastrointestinal and renal . In this section of the thesis, I shall discuss these problems, including the results of a recent large RCT evaluating the administration of NSAIDs in the perioperative period.

#### *Haematological considerations*

NSAIDs inhibit prostaglandin synthesis and hence thromboxane A<sub>2</sub>. The latter is an important mediator of platelet aggregation and is believed to be the principal factor by which NSAIDs impair platelet function.

Of all NSAIDs, ketorolac has been studied in most detail with regard to haemostasis (Noveck 2001). In elderly (aged 65 to 90 years) and non-elderly (aged 18-55 years) patients who received ketorolac 15 mg qds iv and ketorolac 30 mg qds iv, respectively, % platelet aggregation in response to arachidonate was reduced significantly compared with placebo. This change was greater in the elderly population compared with the non-elderly. In addition, despite a large variance, prolonged bleeding times were associated with ketorolac rather than with placebo (Noveck 2001).

Investigations of ketorolac in the perioperative period suggest that ketorolac may increase patients' risk of bleeding in the perioperative period. In an audit of 258

patients undergoing tonsillectomy, the incidence of postoperative haemorrhage was 10.1% in patients who received ketorolac compared with a baseline of 2.2% in the opioid group (Gallagher 1995). Judkins found similar results in her audit of 311 patients after tonsillectomy. The incidence of postoperative bleeding was 17% in patients who were given ketorolac compared with 4.4% who had opioid analgesia (Judkins 1996).

These results have been confirmed in RCTs. After tonsillectomy, ketorolac 1 mg kg<sup>-1</sup> iv has been associated with mean (SD) blood loss of 3 (2) ml kg<sup>-1</sup> (Rusy 1995) and 2.2 (1.9) ml kg<sup>-1</sup> (Splinter 1996) compared with 1 (1) ml kg<sup>-1</sup> in patients receiving rectal paracetamol 35 mg kg<sup>-1</sup>, and 1.3 (0.8) ml kg<sup>-1</sup> in patients treated with codeine 1.5 mg kg<sup>-1</sup> im, respectively. Additional haemostatic measures were also required after administration of ketorolac compared with paracetamol (Rusy 1995), codeine (Splinter 1996) and morphine (Gunter 1995).

Furthermore, diclofenac is associated with an increase risk of haemorrhage after tonsillectomy. After administration of mean (SD) rectal diclofenac 0.77 (0.10) mg kg<sup>-1</sup>, median (interquartile range) blood loss was 1.9 (1.1 to 3.1) ml kg<sup>-1</sup> compared with the significantly lower value of 1.1 (0.7 to 2.0) ml kg<sup>-1</sup> after mean (SD) rectal paracetamol 16 (1.7) mg kg<sup>-1</sup> (Schmidt 2001). The number of haemostatic interventions in patients who received diclofenac was higher but not significantly so compared with the paracetamol group.

Recently, data have become available from a multicentre RCT involving 11 245 patients in 49 European hospitals (Forrest 2002) in the perioperative period. In this

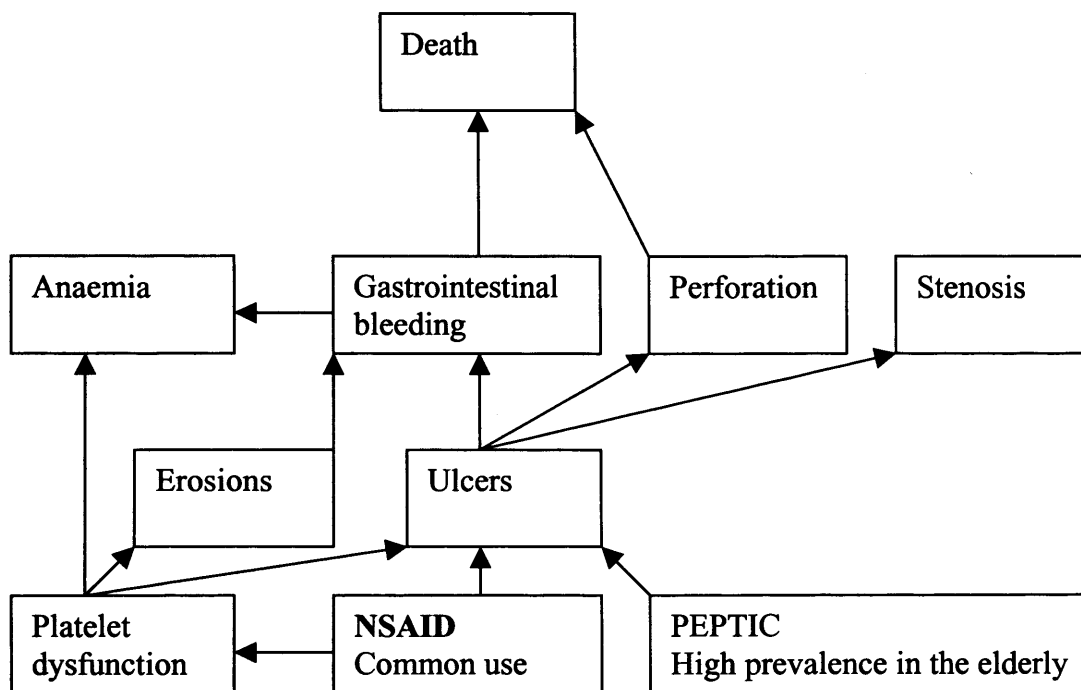
RCT, ketorolac was compared with diclofenac and ketoprofen after orthopaedic, abdominal, gynaecological, urological, plastic, ENT, cardiovascular and thoracic surgery. The median (interquartile range) dose for ketorolac varied from 40(40-70) to 100(70-160) mg, for diclofenac from 75(75-150) to 150(75-225) mg, and for ketoprofen from 200(100-250) to 400(300-400) mg. The most common problem appeared to be increased surgical site bleeding that occurred in 117 patients, of whom 61 received ketorolac and 56 received either ketoprofen or diclofenac. If heparin was given for thromboembolic prophylaxis, then the risk of bleeding was increased compared with no anticoagulant. The odds ratio (95%CI) for surgical site bleeding with a postoperative anticoagulant compared with no anticoagulant was 2.65(1.51-4.67) for ketorolac and 3.58(1.93-6.70) for diclofenac and ketoprofen. Of the four cases of gastrointestinal bleeding, three and one occurred in patients who received ketoprofen and diclofenac, respectively.

In conclusion, there is little doubt that NSAIDs increase patients' risk of bleeding in the perioperative period. For some operative procedures such as tonsillectomy where absolute haemostasis is mandatory, (non-selective) NSAIDs must be administered with caution.

### *Gastrointestinal considerations*

Non-selective NSAIDs are associated with gastrointestinal toxicity eg perforations, ulcers and haemorrhage (McCarthy 1999). The sequence of events has been represented in the diagram below (Fig 1.1).

**Fig 1.1**      **Gastrointestinal toxicity of non-selective NSAIDs**



Factors that influence administration of NSAIDs in the perioperative period are the:

- patients' risk of gastrointestinal toxicity
- NSAID Lanza scores
- dosage of individual NSAIDs.

#### Patients' risk of gastrointestinal toxicity

Patients who come for anaesthesia and surgery may have risk factors for ulcers that preclude their use in the perioperative period. These factors require careful consideration and include: peptic ulcer disease, prior bleeding peptic ulcer disease, advanced age, anticoagulation, steroid use, history of heart disease, comorbid illness, rheumatoid arthritis, ethanol use, helicobacter pylori infection and ulcer cotherapy (Bjorkman 1999).

#### NSAID Lanza Scores

Administration of NSAIDs in the perioperative period may also be influenced by the large variation in gastrointestinal toxicity of different NSAIDs. The potential for toxicity has been defined by their 7-day Lanza scores (Table 1.1) (McCarthy 1999). High scores indicate an elevated risk of gastrointestinal toxicity that may preclude the administration of some NSAIDs in the perioperative period.

**Table 1.1. 7-day Lanza Scores**

<b>Risk</b>	<b>Score</b>	<b>NSAID</b>
High	>3.0	Aspirin, ketorolac, ketoprofen
Moderate	2.0-3.0	Diclofenac, naproxen, indomethacin, ibuprofen > 2400 per day
Low	1.0-2.0	Ibuprofen <1600 mg per day
Very low	<0.50	Meloxicam

#### Dosage of individual NSAIDs

In addition, there is a positive correlation between the dose of NSAID and the incidence of gastric ulcers. For instance, the incidence of gastric ulcers in patients receiving daily ibuprofen 1600 mg, 2400 mg, 3200 mg and 4800 mg is 9.1%, 5.4%, 6.7% and 16.4%, respectively. After daily naproxen 500 mg and 1000 mg, the corresponding incidence has been 5.0% and 10.0%, respectively (McCarthy 1999). If NSAIDs are given to patients in the perioperative period, then adjustment of dose may be necessary particularly in patients who are at risk of gastrointestinal toxicity.

### *Renal complications*

The kidneys are at risk of failure in the perioperative period because of dehydration and hypotension. In addition, NSAIDs are potentially nephrotoxic and thus their administration in the perioperative period should be considered with caution.

NSAIDs have the following pathophysiological effects on the kidney (Brater 1999):

- Reduction in prostaglandin  $E_2$  which leads to a decrease in sodium excretion in the thick ascending limb of the loop of Henle.
- Reduction in prostaglandin  $I_2$  which results in a decrease in renin and aldosterone release, and hence potassium retention at the distal nephron.
- Acute renal failure as a consequence of inhibition of prostaglandin  $I_2$  that maintains renal blood flow when there is a decrease in effective circulatory volume.
- Interstitial nephritis after chronic use
- Analgesic nephropathy and papillary necrosis after chronic NSAID therapy.

Some of these effects have been confirmed by a meta-analysis of 8 placebo controlled RCTs evaluating the effect of NSAIDs in healthy patients, in the perioperative period

(Lee 1999). It was shown that NSAIDs ie ketorolac, diclofenac, indomethacin and ibuprofen were associated with a statistically significant:

- reduction in sodium excretion in urine; weighted mean difference (95% CI) was  $-54$  ( $-103$  to  $-5$ )  $\text{mmol day}^{-1}$ .
- reduction in urinary potassium; weighted mean difference (95% CI) was  $-38$  ( $-56$  to  $-19$ )  $\text{mmol day}^{-1}$ .
- reduction in mean (95% CI) creatinine clearance of  $22$  ( $7$  to  $37$ )  $\text{ml min}^{-1}$ .
- increase in mean (95% CI) serum creatinine of  $15$  ( $2$  to  $28$ )  $\text{mmol l}^{-1}$ .

Despite these possible problems, the possibility of complications associated with NSAIDs appears to low. In a case controlled study in which the investigators compared 10219 patients who received parenteral ketorolac with 10145 patients who had parenteral opioids, no significant difference in risk of acute renal failure was detected. These findings are confirmed by Forrest (Forrest 2001) in a large multicentre RCT. Of 11245 patients who had a NSAID in the perioperative period, there were 10 patients with acute renal failure.

In addition to the above, NSAIDs are associated with other problems and these require some consideration in the perioperative period. In particular, they include a past medical history of aspirin-induced asthma and hypersensitivity to NSAIDs. In the

RCT by Forrest referred to above, severe allergic reactions occurred in 12 patients (Forrest 2001). However, over all, it can be seen that the main problems with NSAIDs are haematological, gastrointestinal and renal.

## **COX-2 inhibitors**

### *Rationale for use of COX-2 inhibitors*

COX-1 is important for producing prostaglandins that are involved in normal physiological functions. The activity of COX-2 is cytokine-induced producing prostaglandins that mediate pain and inflammation. Thus, in anaesthetic practice, inhibition of COX-2 enzymes is desirable because of possible analgesic and anti-inflammatory effects (Ng, Smith, Davidson 2003) (Ehrich 1999). Inhibition of COX-1 enzyme is theoretically undesirable owing to the reduction of prostaglandins that maintain normal body functions eg maintenance of gastrointestinal integrity. Thus, although traditional non-selective NSAIDs provide postoperative analgesia, they are associated with adverse effects that are related, in part, to COX-1 inhibition. In particular, these effects are gastrointestinal ulceration, bleeding and renal failure.

In the following section I shall be consider their pharmacology, possible benefits and analgesic efficacy.

### *Pharmacology of COX-2 inhibitors*

Celecoxib, rofecoxib and valdecoxib are the currently available COX-2 inhibitors. They are administered orally and their pharmacological properties (Gajraj 2003) are compared below (Table 1.2.).

**Table 1.2. Comparison of COX-2 inhibitors**

	<b>Celecoxib</b>	<b>Rofecoxib</b>	<b>Valdecoxib</b>
Molecular weight	381	314	314
Route of administration	Oral	Oral	Oral
Dosage in an adult (mg)	200-400	25-50	20-40
Elimination half life (h)	12	17	8-11
Volume of distribution (l)	400	86-89	86
Protein binding (%)	98	87	98
Metabolism	Cytochrome P450 (2C9)	Cytosolic enzymes	Cytochrome P450 (3A4 and 2C9)
Metabolite	Inactive	Active	Active

In addition, parecoxib is a new COX-2 inhibitor preparation for parenteral administration. It is a prodrug that is hydrolysed in the liver to its active moiety, valdecoxib. Time to peak plasma concentration, peak plasma concentration and

terminal elimination half life of valdecoxib following 50 mg of parecoxib iv has been shown to be 0.6 h,  $1.02 \text{ mg l}^{-1}$  and 7.88 h, respectively (Cheer 2001).

Administration of COX-2 inhibitors with other drugs may require some vigilance. In general, they appear to increase serum warfarin (Mersfelder 2000) and lithium levels (Lundmark 2002). Owing to their nonarylamine structure that is related to sulphonamides, celecoxib and valdecoxib are contraindicated in patients with sulphonamide allergy (Gajraj 2003).

### *Possible benefits of COX-2 inhibitors*

In the perioperative period, patients are at risk of bleeding and may have comorbidity such as peptic ulcer disease. In this section, I shall discuss the possible benefits of COX-2 inhibitors over non-selective NSAIDs, and hence reasons for their administration in the perioperative period.

#### Gastrointestinal considerations

In comparison with patients who do not take NSAIDs, it has been estimated that 1 in 1200 patients taking NSAIDs for at least 2 months will die from gastroduodenal complications (Tramer 2000). It has been estimated that there will be 2000 deaths per year attributable to NSAIDs in the UK. Consequently, whilst NSAIDs may be useful analgesics, they are not without this life-threatening effect.

From data obtained on patients with arthritis, it appears that COX-2 inhibitors are safer than non-selective NSAIDs. Two important RCTs, the CLASS (Silverstein 2000) and the VIGOR (Bombardier 2000), have shown that celecoxib and rofecoxib are associated with significant reductions in upper gastrointestinal complications compared with non-selective NSAIDs. In a more recent systematic review comprising 9 RCTs in which 15187 patients were enrolled, it was shown in patients treated for osteoarthritis or rheumatoid arthritis that the relative risk (95% CI) of any upper gastrointestinal event with celecoxib compared with a NSAID was 0.54(0.42-0.71) (Deeks 2002). In a placebo case controlled population based study in Ontario, Canada in 2000-1, the adjusted risk ratios (95% CI) of gastrointestinal haemorrhage for non-

selective NSAIDs, a combination of diclofenac and misoprostol, rofecoxib and celecoxib were 4.0(2.3-6.9), 4.6(2.5-8.2), 3.5(2.4-5.0) and 1.7(1.1-2.6), respectively (Mamdani 2002). These findings are confirmed by data in other clinical studies and published as abstracts (Goldstein 2001) (Goldstein, Zhao 2001) (Agrawal 2001)(Goldstein, Eisen 2001).

Thus, in the perioperative period, COX-2 inhibitors may be useful particularly in patients who have risk factors for gastrointestinal toxicity.

### Haematological and cardiovascular considerations

Possible cardiovascular events of selective NSAIDs have also been analysed extensively. In the VIGOR study, it was found that the rates of cardiovascular events and in particular myocardial infarction were significantly higher in patients having rofecoxib than in those having naproxen (Bombardier 2000). The relative risk of myocardial infarction (95% CI) was 0.2 (0.1-0.7) in the naproxen group, suggesting a coronary protective effect presumably from sustained platelet inhibition that is not characteristic of COX-2 inhibitors. Indeed, in a study of parecoxib 40 mg bd for 8 days in patients aged 18-95, ketorolac 15 mg qds for 5 days in patients aged 65-95 years and ketorolac 30 mg qds for 5 days in patients aged 18-55 years, it was shown that parecoxib had minimal effect on platelet aggregation, whereas ketorolac produced a significant reduction in platelet aggregation (Noveck 2001). Significantly longer bleeding times were also noted in the ketorolac groups compared with patients treated with parecoxib.

In an attempt to disprove the hypothesis of higher cardiovascular events in patients taking rofecoxib, there has been an assessment of cardiovascular thrombotic events in 23 phase IIb to V rofecoxib studies of 28 000 patients (Konstam 2001). These events were defined by the Antiplatelet Trialists' Collaboration and were cardiovascular, haemorrhagic and unknown death, non-fatal myocardial infarction and non-fatal stroke. It was shown that the relative risk of an event between rofecoxib and placebo, between rofecoxib and non-naproxen NSAIDs, and between rofecoxib and naproxen was 0.84(0.51-1.38), 0.79(0.40-1.55) and 1.69(1.07-2.69), respectively. From these findings, it may be possible to conclude that naproxen has no significant cardiovascular protective effect compared with rofecoxib and that rofecoxib may

increase the risk of a cardiovascular event compared with naproxen. In a recent retrospective study, there was some evidence that any risk of a cardiovascular event with rofecoxib may be related to its dose (Ray 2002). In comparison with non-users and celecoxib users respectively, the relative risk (95% CI) of a serious cardiovascular event was 1.93(1.09-3.43) and 2.20(1.17-4.10) in patients taking rofecoxib in doses exceeding 25 mg. There was no increased risk of these events in patients receiving lower doses of rofecoxib, or in those with doses of celecoxib > 300 mg, naproxen  $\geq$  1000 mg and ibuprofen  $\geq$  1800 mg.

Over all, COX-2 inhibitors appear to spare platelet function compared with NSAIDs. On the one hand, this effect may be useful when postoperative haemorrhage is a particular concern eg post tonsillectomy and after plastic surgery; on the other hand, it may increase the risk of myocardial ischaemic in patients with ischaemic heart disease.

### Renal considerations

The evidence for any sparing of renal function of COX-2 inhibitors compared with non-selective NSAIDs is sparse. The CLASS study did show that the incidence of increased creatinine and hypertension was significantly lower in patients receiving celecoxib compared with those having NSAIDs (Silverstein 2000). However, these benefits were not detected in another RCT (Simon 1999). It would appear that precautions taken for non-selective NSAIDs are necessary for COX-2 inhibitors, in the perioperative period.

*Analgesic outcomes*

The majority of studies comparing the analgesic efficacy of COX-2 inhibitors with non-selective NSAIDs has been in patients with chronic pain. In a systematic review of RCTs examining patients with arthritic pain (Deeks 2002) and in studies on patients with primary dysmenorrhoea (Morrison 1999)(Daniels 2002), COX-2 inhibitors were shown to have similar analgesic effects compared with existing NSAIDs.

In the perioperative period, there is evidence that COX-2 inhibitors are effective for analgesia. After molar teeth extraction and bunionectomy, valdecoxib 20 mg, 40 mg and 80 mg were associated with increased time to rescue analgesia and dose dependent reduction in pain intensity, in a placebo controlled RCT (Desjardins 2002). In a RCT of patients who had arthroscopic knee surgery, rofecoxib 50 mg given preoperatively was associated with significantly reduced pain intensity and rescue analgesic consumption, compared with placebo (Reuben 2002). When rofecoxib 50 mg was given to patients an hour prior to spinal fusion surgery, 24 morphine consumption in the postoperative period was reduced by 39% compared with placebo (Reuben 2000). Furthermore, in this RCT, rofecoxib 50 mg was more effective than celecoxib 200 mg in reducing 24 h morphine consumption and pain intensity. This difference may be explained by differences in pharmacokinetics of the two drugs. Celecoxib has a larger volume of distribution compared with rofecoxib and so perhaps a higher initial dose ie 400 mg would have been necessary to achieve similar serum concentrations and hence comparable analgesic effects.

In addition, rofecoxib 50 mg has been shown to be effective for analgesia after lower abdominal surgery (Shen 2001) and dental surgery (Chang 2002). However, the disadvantage of rofecoxib, celecoxib and valdecoxib in general anaesthetic practice is that they are oral preparations. In the perioperative period, especially in emergency situations, some patients may have PONV and delayed gastric emptying. Recently, a new COX-2 inhibitor for parenteral use has been released. It is called parecoxib, and in a placebo controlled RCT of patients having oral surgery, it was associated with reduction in time to rescue analgesia, pain intensity as well as proportion of patients requiring rescue analgesia (Desjardins 2001).

#### **1.3.4. Multimodal analgesia**

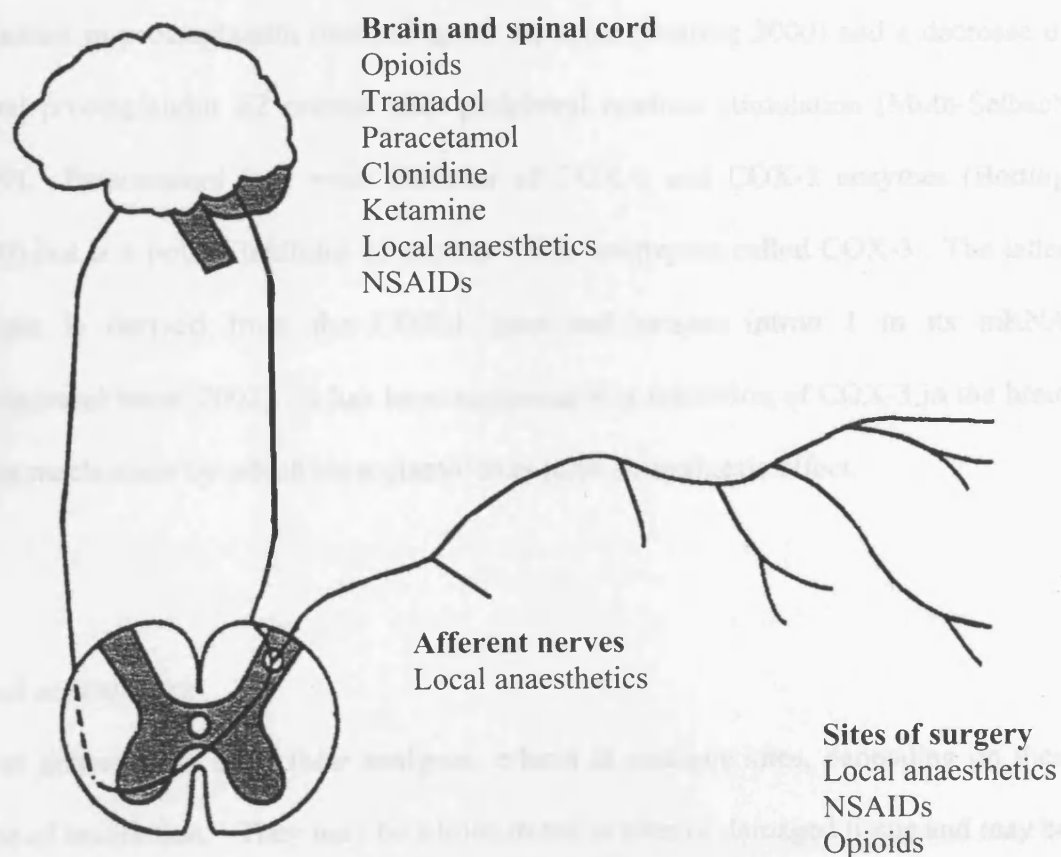
Multimodal analgesia is the term used to describe the provision of pain relief using two or more methods of analgesia (Sinatra 2002). It has been associated with a reduction in the extent of moderate to severe pain (Caumo 2002) and it is useful for two main reasons:

- After surgery, patients experience pain as a consequence of complex processes that occur in multiple areas ie sites of tissue trauma, along peripheral nerves, in the spinal cord and in the brain. Individual drugs act at different sites in the nociceptive pathway and so their use in combination may be associated with more effective and measurable analgesia compared with their administration in isolation (Staats 2002). The analgesic effect may be synergistic rather than purely additive. For instance, in a qualitative review of RCTs of postoperative analgesia, combinations of NSAID with paracetamol were shown to be significantly more effective for analgesia than paracetamol alone (Hyllested 2002).
- Analgesic and adverse effects associated with individual drugs eg morphine are dose dependent. A multimodal approach enables individual drugs to be used at lower doses that are adequate to produce analgesia whilst avoiding higher doses that are associated with adverse effects.

## Drugs used for multimodal analgesia and their sites of action

In anaesthetic practice, postoperative analgesia is achieved commonly by more than one group of drugs (Jin 2001). The sites of action of some of these drugs are illustrated below.

**Fig 1.2. Sites of drug action**



### *NSAIDs*

Analgesia associated with NSAIDs is attributable to their inhibition of COX-2 enzymes and hence the control of production of prostaglandins that mediate inflammation. The periphery is the main target for NSAIDs where prostaglandins are released from nociceptive neurones in response to tissue damage and bradykinin. In addition, owing to the presence of COX-2 enzymes in glial cells and dorsal horn neurons, NSAIDs may have a central modulatory role.

### *Paracetamol*

Paracetamol is a simple analgesic that appears to act centrally. It is associated with a reduction in prostaglandin metabolites in the urine (Botting 2000) and a decrease in spinal prostaglandin E<sub>2</sub> release after peripheral noxious stimulation (Muth-Selbach 1999). Paracetamol is a weak inhibitor of COX-1 and COX-2 enzymes (Botting 2000) but is a potent inhibitor of another COX isoenzyme called COX-3. The latter protein is derived from the COX-1 gene and retains intron 1 in its mRNA (Chandrasekharan 2002). It has been suggested that inhibition of COX-3 in the brain is the mechanism by which paracetamol may have an analgesic effect.

### *Local anaesthetics*

Local anaesthetics exert their analgesic effects at multiple sites, depending on their route of instillation. They may be administered to sites of damaged tissue and may be given to block peripheral nerve conduction. In addition, they are used often for

central neural axial blockade and they have a central analgesic effect when they are given intravenously.

### *Tramadol*

Analgesia associated with tramadol occurs because of elevation of central synaptic levels of norepinephrine and 5HT, as well as action on opioid receptors (Shipton 2000). The (-) enantiomer inhibits norepinephrine reuptake and causes increased stimulation-evoked release by presynaptic autoreceptor activation. The (+) enantiomer is a weak  $\mu$  receptor agonist. Also, it inhibits the central neuronal uptake of 5HT and stimulates presynaptic release of 5HT. Thus, tramadol appears to have useful multiple complementary non-opioid and opioid analgesic mechanisms.

### *Opioids*

The analgesic effects associated with opioids occur as a result of their action on receptors in the brain and spinal cord. In addition, owing to the presence of peripheral opioid receptors, some investigators have administered opioids to sites of tissue trauma eg during knee arthroscopy. It would appear, however, that peripheral opioids have not been associated with useful analgesia. (Rosseland 1999, Varrassi 1999, Yarussi 1999).

### *Clonidine*

Clonidine is an  $\alpha_2$  agonist that is used as an analgesic adjunct (Sandler1996). In common with other  $\alpha_2$  agonists including dexmedetomidine, it acts at receptors in both the spinal cord and brain. It may be administered by the systemic, oral, epidural or intrathecal route (Eisenach 1996).

### *Ketamine*

Ketamine exerts its analgesic effects by being an antagonist at N-methyl D-aspartate receptors in the brain and spinal cord (De Beer 2003). It may be administered systemically as well as by the epidural route.

Currently, because of the lack of analgesic drugs devoid of side effects, multimodal analgesia is invariably employed for pain relief after surgery. A combination is chosen from the following:

- An opioid, usually morphine for major surgery or fentanyl for more minor surgery and day case surgery.
- A local anaesthetic block, usually spinal or epidural analgesia for major abdominal surgery, plexus or isolated nerve block for limb surgery, and nerve blocks or infiltration for day surgery.

- A NSAID, frequently in the form of a suppository for major surgery before the patient commences normal eating and drinking or by the oral route for more minor surgery.
- Paracetamol for minor surgery or the later postoperative period following major surgery.

Any combination of the above may be used depending on the type of surgery and the age and physical state and coexisting medical condition of the patient. It will be seen that the objective of the studies described in the thesis is to examine some novel combinations used for postoperative pain relief.

## **1.4. Opioid analgesia and management of PONV**

### **1.4.1. Introduction**

Morphine and other strong opioids are associated with adverse effects such as PONV. In some instances, patients who have PONV are afraid to administer themselves with opioids via the PCA device. In a prospective survey of 10 811 patients, it was shown (Myles 2000) that severe nausea and vomiting were associated with patient dissatisfaction; OR(95% CI) was 4.09(3.18-5.25). Thus effective management of PONV go hand in hand with the provision of adequate postoperative analgesia. In this section, the latest literature on effective management of PONV has been reviewed.

Evidence on outcome of different treatments for PONV has been collated in quantitative systematic reviews (meta-analysis) of many double blind RCTs. Although they represent a high level of evidence some assessment of the treatment effects of the individual trials must be made before making a decision on whether the pooled results are valid. Over all applications of quantitative systematic reviews as well as their limitations have been discussed extensively in a recent article by Choi (Choi 2000).

Trials that have had event rates of 20% to 60% for early PONV (0-6 h) and 40% to 80% for late PONV (0-48 h) have been included in some systematic reviews, excluding studies with extreme values that were not deemed to reflect the over all clinical situation. Treatment effect in many of these reviews has been quantified in terms of relative benefit, relative risk or odds ratio and also absolute risk reduction. The relative benefit, relative risk or odds ratio allows a relative comparison of the

outcome of one treatment over another but does not take into account the magnitude of the problem. However, the absolute risk reduction does take into account the importance of the treatment effect, providing the clinician with more information from which to decide if the treatment is worth administering. The reciprocal of the absolute risk reduction gives the term “Number Needed to Treat”(NNT). The NNT is the number of patients who must be treated to obtain one additional favourable outcome (Sackett 2000). More efficacious treatments have a low NNT while less useful treatments have a high NNT. All treatments have adverse effects, and in a similar way to the above consideration of benefits, “Number Needed To Harm” (NNH) can be obtained from the reciprocal of absolute risk increase.

#### **1.4.2. Factors that influence the occurrence of PONV**

PONV is more common in females and patients with a previous history of PONV or motion sickness. It appears to be associated with strabismus surgery, adenotonsillectomy, orchidopexy and prolonged surgery. Other factors predisposing to its occurrence are use of etomidate, opioids, pancuronium and the use of atropine and neostigmine (Ogilvy 1995). Propofol on the other hand has the opposite effect, and in a systematic review of 84 RCTs involving 6069 patients, its effect of on early and late PONV was assessed (Tramer, Moore, McQuay 1997;78:247-55). When used for maintenance instead of inhalation agents, propofol had a NNT (95% CI) of 4.9 (3.7-7.1), and 7.1 (3.4- $\infty$ ) for early and late PONV, respectively, suggesting that any antiemetic advantage is short lived. Propofol used solely for induction did not confer an advantage over other intravenous agents. In a reassessment (Tramer, Moore, McQuay 1997;78:256-9) of a systematic review of RCTs in which use of nitrous oxide was assessed (Tramer 1996), it was shown that omission of nitrous oxide has beneficial effects on early (NNT 4.8(3.6-7.3)) and late vomiting (NNT 5.6 (3.9-10)), but not early (NNT 9.1(4.1- $\infty$ )) or late nausea (NNT  $\infty$  (80)).

### **1.4.3. Methods to prevent and treat PONV**

A management plan for prevention of PONV has been summarised in Table 1.2. Techniques to minimise PONV may be classified into pharmacological agents and non-pharmacological methods. Studies on readily available pharmacological agents have compared the use of single agents versus placebo; combination of agents versus single agents; and administration of an antiemetic with an opioid via a PCA device. In addition, data have been available concerning the possible antiemetic effect of 80% inspired oxygen compared with 30% (Greif 1999). In this RCT, oxygen was given intraoperatively and for the first two postoperative hours in patients undergoing colorectal surgery, it has been found that the higher oxygen concentration had an antiemetic effect.

**Table 1.3. Management of PONV**

<b>Plan</b>	<b>Example</b>
Identify the patient at risk	<p>Female gender</p> <p>Non-smoker</p> <p>Positive history of PONV</p> <p>Positive history of motion sickness</p> <p>Duration of anaesthesia &gt; 60 minutes</p>
Use an antiemetic anaesthetic technique	<p>Use propofol</p> <p>Minimise use of emetogenic agents e.g.: opioids, etomidate</p>
Consider specific antiemetic treatments	<p><i>Individual pharmacological agents</i></p> <p>NK1 antagonists</p> <p>5HT<sub>3</sub> antagonists</p> <p>Dexamethasone</p> <p>Droperidol</p> <p>Cyclizine</p> <p><i>Combination agents</i></p> <p>5HT<sub>3</sub> antagonists with cyclizine</p> <p>5HT<sub>3</sub> antagonist with dexamethasone</p> <p>5HT<sub>3</sub> antagonist with NK1 antagonist</p> <p><i>Physical therapy</i></p> <p>Acupuncture</p>

### *NK-1 receptor antagonists*

NK-1 antagonists are thought to act by blocking the effect of substance P on NK-1 receptors. (Otsuka 1993). For prevention of PONV, evidence from a double blind RCT of females listed for abdominal hysterectomy demonstrated that 100 mg or 200 mg of oral CP122721, administered 60 to 90 minutes preoperatively, was more effective than placebo for prevention of PONV within 8 h and 72 h into the postoperative period (Gesztesi 2000). Within the first 8 h the higher dose of this NK-1 antagonist was more effective than the lower dose (the incidences of PONV being 10% and 33% respectively). This benefit was not demonstrable within 72 h. It is possible that further clinical studies may reveal a role for NK-1 antagonists in patients at high risk of PONV.

### *5HT<sub>3</sub> antagonists*

Although several 5HT<sub>3</sub> antagonists have been evaluated, ondansetron has been studied most extensively. The efficacy of ondansetron has been assessed for both prophylaxis and also as treatment of PONV. In a meta-analysis of 53 placebo-controlled RCTs involving 7177 patients, 24 different ondansetron regimens were evaluated (Tramer, Reynolds 1997) for the prevention of PONV. Although a broad range of NNTs were obtained, ondansetron showed treatment benefit (NNT 5-6) in doses of 8 mg iv and 16 mg orally, for prevention of early and late PONV. In addition, there was a significant increased risk of elevated liver enzymes (NNH of 31) and headache (NNH of 36).

The issue on whether ondansetron is effective in preventing PONV in high risk patients has also been addressed. In a meta-analysis of RCTs, ondansetron 4 mg and 8

mg iv showed increased effectiveness for prevention of PONV in patients with motion sickness compared with patients without this history (Figueredo, Canosa 1999;16:556-4.). The pooled odds ratios (95% CI) were 2.07(1.69-2.52) and 2.19 (1.5-3.19) for the two respective doses. In another meta-analysis comparing patients with and without a previous history of PONV, there was no significant difference in effectiveness of ondansetron for vomiting within the first 24 hours postoperatively, at a dose of 4 mg iv (Figueredo, Canosa 1999;43:637-44). There was a trend to effectiveness at 8 mg iv but this effect was not statistically significant.

Ondansetron has been compared with other individual antiemetic drugs in addition to placebo. In a meta-analysis (Domino 1999) of 23 RCTs with 3863 patients comparing ondansetron with droperidol, and 19 RCTs of 2502 patients comparing ondansetron with metoclopramide, the pooled odds ratio (95% CI) for prevention of vomiting was 0.70 (0.52-0.94) and 0.43 (0.31-0.61), respectively. The corresponding odds ratios (95% CI) for prevention of nausea were 0.99 (0.66-1.47) and 0.70 (0.45-1.10), demonstrating that ondansetron was significantly more effective than either droperidol or metoclopramide in preventing vomiting, but not nausea. Doses of all drugs varied: ondansetron 4 mg to 8 mg, and 0.10 mg kg<sup>-1</sup> to 0.15 mg kg<sup>-1</sup>; droperidol 0.625 mg to 2.5 mg, and 20 µg kg<sup>-1</sup> to 75 µg kg<sup>-1</sup>; metoclopramide 10 mg, and 0.25 mg kg<sup>-1</sup> to 0.5 mg kg<sup>-1</sup>. This mixed effectiveness of ondansetron over droperidol contrasts with another quantitative systematic review, in which data in adults from 20 RCTs showed that the odds ratio (95% CI) was 0.56 (0.41-0.76) and NNT (95% CI) was 12 (7-32) in favour of ondansetron over droperidol. Data concerning doses administered were not available for assessment (Loewen 2000).

In addition to its role in prevention of PONV, ondansetron may be administered to treat established PONV. In a quantitative systematic review (Tramer, Moore, Reynolds, McQuay 1997) of 7 RCTs, it was shown that intravenous ondansetron was effective compared with placebo for the treatment of established early and late PONV. For treatment of early PONV, the NNT (95% CI) was 3.8(2.6-6.6), 3.2(2.3-5.2), 3.1(2.4-4.5) with 1 mg, 4 mg and 8 mg of ondansetron respectively. The respective NNT values at the corresponding doses for treatment of established late PONV were 4.8(3.5-7.9), 3.9(3.0-5.7) and 4.1(3.1-6.2). Thus, at doses used clinically there is no additional benefit in using higher doses of ondansetron for treatment of established PONV. In summary, ondansetron is an effective antiemetic for prevention and treatment of PONV.

### *Dexamethasone*

Dexamethasone in doses of 8 mg to 10 mg, and 1 mg kg<sup>-1</sup> to 1.5 mg kg<sup>-1</sup> has been evaluated in a quantitative systematic review (Henzi 2000). Results from 15 placebo RCTs show that dexamethasone was effective for prevention of early and late PONV. The NNT (95% CI) for prevention of early and late vomiting in children and adults was 7.1 (4.5-18) and 3.8 (2.9-5.0), respectively. Data for nausea were available in adults but not children; the NNT for early and late nausea was 5.0 (2.1-22.2) and 4.3 (2.3-26). Analysis of other trials in this review showed that antiemetics such as ondansetron 4 mg iv, granisetron 3 mg iv and perphenazine 70 µg kg<sup>-1</sup> were more effective than dexamethasone for prevention of PONV.

Other issues of dexamethasone concern the dose and timing of administration. In a double blind placebo controlled RCT of females undergoing thyroidectomy it was found that the minimum effective dose for prevention of PONV was dexamethasone 5 mg iv given at induction of anesthesia (Wang, Ho, Lee 2000). Furthermore, in comparison with administration at the end of surgery, dexamethasone 10 mg given at induction of anaesthesia was associated with greater reductions in incidence of PONV and rescue antiemetic consumption (Wang, Ho, Tzeng 2000).

### *Droperidol*

Droperidol was once a well established antiemetic but it is now no longer available in the UK. It is a butyrophenone that may cause dose-dependent sedation and drowsiness. Therefore the main concern with its use was the minimum dose required to prevent PONV. In a systematic review (Henzi, Sonderegger 2000), it was shown that 0.5 mg to 0.75 mg of droperidol was sufficient to prevent early nausea and that at least 1 mg to 1.25 mg was required for late nausea, in adults. For early vomiting, at least 1 mg to 1.25 mg iv of droperidol was required compared with a lower dose of 0.5 mg to 0.75 mg iv for late vomiting in adults. In children, there was a dose dependent effect for early and late vomiting and the relative risk was clearly in favour of droperidol compared with placebo, at doses of  $50 \mu\text{g kg}^{-1}$  to  $75 \mu\text{g kg}^{-1}$  compared with  $10 \mu\text{g kg}^{-1}$  to  $20 \mu\text{g kg}^{-1}$ .

### *Metoclopramide*

Metoclopramide is an antagonist at central dopaminergic receptors, central and peripheral 5HT<sub>3</sub> receptors and peripheral 5HT<sub>4</sub> receptors. In a systematic review of 66 placebo controlled RCTs involving 6266 patients, no antiemetic effect was detected within six hours postoperatively and at 48 hours (Henzi, Walder, Tramer 1999). In adults, doses varied from 5 mg to 35 mg via iv, im, oral and intranasal routes. In children the doses were 0.1 mg kg<sup>-1</sup> to 0.5 mg kg<sup>-1</sup> given iv in all but one trial. Even at high doses, adverse reactions such as extrapyramidal symptoms, sedation, drowsiness, dizziness, vertigo and headache were uncommon.

### *Combination antiemetic therapy*

Combination antiemetic therapy or “balanced anti-emesis” (Heffernan 2000) is another technique that some investigators have been studying for prevention of PONV. Combinations of a 5HT<sub>3</sub> receptor antagonist (ondansetron 4 mg; granisetron 3 mg or 20 µg kg<sup>-1</sup> to 40 µg kg<sup>-1</sup>) with either dexamethasone 8 mg (Henzi, Walder, Tramer 2000) or cyclizine 50 mg iv (Ahmed 2000) have been shown to be associated with increased effectiveness compared with the individual 5HT<sub>3</sub> antagonist. Pueyo (Pueyo 1996) compared a combination of intravenous ondansetron 4 mg and droperidol 3.75 mg with ondansetron 4 mg and found that the combination was associated with increased effectiveness. However, Bugedo (Bugedo 1999) found no advantage after a combination of ondansetron 4 mg and droperidol 2.5 mg compared with ondansetron 4 mg. In a meta-analysis of RCTs in which a combination of droperidol and a 5HT<sub>3</sub> antagonist was compared with the individual agent, it was found that there was no significant advantage for the combination (Eberhart 2000).

Combination antiemetic therapy for PONV involving the administration of 200 mg of oral NK-1 antagonist CP1222721 and 4 mg iv of ondansetron has been compared with the individual drugs in a double blind RCT (Gesztési 2000). There was a significant improvement in the median emesis-free time for 75% of patients in the combination group compared with the patients receiving CP1222721 or ondansetron separately. No significant difference in nausea scores between the three groups within 8 and 24 hours was detected. However, the incidence of emesis within 24 hours was significantly less with the combination compared with ondansetron but not with CP1222721. Another NK-1 antagonist has been assessed recently in patients receiving chemotherapy. The addition of NK-1 antagonist, L754030 300 mg to 400 mg, to granisetron  $10 \mu\text{g kg}^{-1}$  iv and dexamethasone 20 mg orally was found to produce significant antiemetic benefits (Navari 1999).

In summary, it appears that combination therapy involving the addition of some agents such as dexamethasone, cyclizine or an NK-1 antagonist to a 5HT<sub>3</sub> antagonist provides additional prophylaxis against PONV compared with the individual 5HT<sub>3</sub> antagonist. For PONV that is difficult to treat, a combination of three drugs may be necessary eg antagonists at 5HT<sub>3</sub>, NK-1 and dopamine receptors.

#### *Prophylactic antiemetics during PCA opioids*

The effectiveness of administering an antiemetic with an opioid via a PCA device has been assessed in a quantitative systematic review of 14 eligible RCTs of 1117 patients (Tramer, Walder 1999). Morphine was used in all but one RCT. Of the various

antiemetic agents such as hyoscine, propofol, metoclopramide, clonidine, promethazine, droperidol, ondansetron and tropisetron, the most frequently used were the latter three drugs. Droperidol, ondansetron and tropisetron were found to be effective for prevention of PONV and their respective NNT (95% CI) was 2.8(2.1-3.9), 2.9 (2.1-4.7) and 4.7 (3.0-11).

### *Acupuncture*

The effect of stimulation of the P6 acupuncture point on PONV was assessed in a meta-analysis of 19 RCTs involving 1679 patients undergoing tonsillectomy, laparoscopy, Caesarean section as well as gynaecological and general surgery (Lee 1999). Acupuncture varied in terms of type, method, timing and duration of administration. Manual acupuncture, electroacupuncture, transcutaneous electrical stimulation and acupressure to P6 were given preoperatively, intraoperatively and postoperatively. In addition, the duration of treatment varied from five minutes to seven days. It was found that this non-pharmacological technique had significant benefit compared with no treatment or sham treatment in adults for preventing early PONV. For early nausea, the relative risk (RR) (95% CI) was 0.34 (0.20-0.58) with a NNT (95% CI) of 4 (3-6). The RR (95% CI) for early vomiting was 0.47 (0.34-0.64) and the NNT (95% CI) was 5 (4-8). There was no treatment benefit for late vomiting (0-48 hours) in adults, and early and late vomiting in children. In seven trials within this meta-analysis, stimulation of P6 and use of antiemetics (metoclopramide, cyclizine, droperidol) were compared and it was found that there was no significant difference in prevention of early and late vomiting in adults.

#### **1.4.4. Predictive scoring systems**

In making a decision on whether to provide therapy to prevent the occurrence of PONV, assessment of factors that predict its occurrence are required. An ideal scoring system would be highly discriminative for all types of patients undergoing all forms of surgery, in any hospital, and should be easy to apply. Some scoring systems have identified predictive factors by logistic regression analysis and the user has to go through a complex process taking into account the weighting of each factor (Eberhart 2000). Recently however, a simplified scoring system based on four risk factors has been evaluated in patients having orthopaedic, ophthalmic, otolaryngological and general surgery. These factors of equal weighting comprised: female gender, history of motion sickness or PONV, non-smoking and use of intraoperative opioids. The ability of this scoring system to discriminate between patients who would and would not have PONV, has been quantified by the area under the Receiver Operator Curve, a plot of the true positive rate against the false positive rate. For a variety of operations, it was found that in the presence of none, one, two, three and four risk factors, the incidence of PONV was 10%, 21%, 39% 61% and 79% respectively (Apfel 1999). In making a decision on whether to administer medication for prevention of PONV, use of this type of simple scoring system would be helpful to the anaesthetist.

### **1.5. Changes in surgical practice and outcome**

Use of minimally invasive surgical techniques and increased practice of day surgery are two major factors that have influenced surgical outcome over the past decade (Hunter 2001). An operation that demonstrates this change is cholecystectomy. Of 30968 cholecystectomies in a recent population based study, 78.7% were performed laparoscopically (Hannan 1999). The main finding of this study was that the risk adjusted odds ratio of 0.34 for mortality was significantly ( $P < 0.0001$ ) lower after laparoscopic cholecystectomy than after open cholecystectomy. These results concur with the lower mortality rates for laparoscopic cholecystectomy in a previous meta-analysis comprising 126 studies (Shea 1996).

For surgically uncomplicated laparoscopic cholecystectomy and other types of day surgery, important outcome measures have been duration of hospital stay, unanticipated admissions, time to recreational activity and return to work. In an Australian survey of over 1000 patients, mean length of stay was 2.6 days after laparoscopic cholecystectomy compared with 8.7 days after open cholecystectomy (Vandernbergh 1995). For surgical procedures performed on an ambulatory basis, it has been shown by logistic regression analysis that unanticipated hospital admissions were significantly more likely in patients who had excessive pain, nausea, vomiting, drowsiness and dizziness (Fortier 1998). Other predictive factors were long duration of surgery, surgery finishing after 3 pm, postoperative bleeding, male sex and ASA II or III categories. In addition, it was estimated that if 95% of open cholecystectomies were done laparoscopically, then 133285 hospital bed-days and 500 000 work-days each year would be saved.

Despite the favourable outcomes cited above, the evidence in favour of laparoscopic cholecystectomy has not been as definitive as that for laparoscopic appendicectomy and laparoscopic inguinal hernia repair. Despite higher rates of common bile duct injury compared with open cholecystectomy, it has always been assumed by surgeons that laparoscopic cholecystectomy would be beneficial over all. However, this view was unclear for laparoscopic appendicectomy and laparoscopic hernia repair and so clinical trials comparing them with the open method were required. It has now been shown that both laparoscopic appendicectomy and laparoscopic hernia repair (EU Trial 2000) take longer and cost more to perform than their respective open procedures. However, after both laparoscopic operations, time for rehabilitation was shorter and the incidence of wound infection was reduced following laparoscopic appendicectomy compared with open appendicectomy (Hunter 2001).

With this continuing change in practice from open to minimally invasive surgery, it has been necessary to analyse specific anaesthetic factors that minimise patient morbidity. In a recent prospective study of 200 patients, it has been shown that pain in addition to fatigue and preoperative expectations were the main factors determining the duration of convalescence after laparoscopic cholecystectomy (Bisgaard 2001). In patients undergoing open inguinal herniorrhaphy under local anaesthesia as a day case, pain was shown to be the main factor impairing activities of daily living (Callesen 1999). Thus, it can be seen that the provision of non-sedating and effective postoperative analgesia is vital to facilitate rehabilitation after surgery and anaesthesia.

## **Part 2            Scope of this thesis**

### **1.6.            Hypothesis**

Do novel methods of analgesia benefit the patient after common painful surgical procedures?

Common surgical procedures such as TAH, laparoscopic cholecystectomy and laparoscopic sterilisation are associated with considerable pain and in most instances, opioid analgesia is required. However, administration of opioids is associated with adverse effects such as sedation, nausea, and PONV. Thus, other methods of analgesia that obviate the use of strong opioids would be desirable.

In this thesis I shall describe studies designed to see if administration of local anaesthetics and NSAIDs have any utility in minimising the dosage of opioids and hence their concomitant adverse effects in two clinical situations:

- after major abdominal surgery
- after minor minimally invasive surgery.

## **1.7. Administration of local anaesthetics**

### **Major abdominal surgery**

It has previously been shown that either intraperitoneal or incisional administration of local anaesthetics has no significant morphine sparing effect after major abdominal surgery such as TAH. In one of the RCTs of this thesis, we have investigated if both intraperitoneal and incisional administration of local anaesthetics reduces morphine consumption after TAH. We have also assessed if patient morbidity such as pain intensity, sedation as well as PONV can be reduced.

### **Minimally invasive surgery**

Laparoscopic cholecystectomy and gynaecological laparoscopic sterilisation are two examples of common minimally invasive surgical procedures that are painful and may require administration of parenteral morphine.

In previous studies of patients having laparoscopic cholecystectomy, there has been controversy concerning the utility of intraperitoneal administration of local anaesthetics (Moiniche 2000). The inability to demonstrate definitive analgesia may be attributable to the fact that cutaneous sites were not infiltrated with local anaesthetics. Thus, in one of the RCTs of this thesis, we have investigated if intraperitoneal administration of levobupivacaine with epinephrine has morphine

sparing effects following laparoscopic cholecystectomy. In all patients, local anaesthetics were administered to the incisional sites.

Laparoscopic sterilisation is associated with spasmodic pain that may require administration of morphine postoperatively. We have used the transcervical route to administer local anaesthetics prior to application of Filshie clips. In theory, this method allows direct application of local anaesthetic to the site of nociceptive stimuli. In addition, we have compared the administration of local anaesthetics with that of papaverine, a smooth muscle relaxant that has been used to reduce smooth muscle spasm in other clinical situations eg ureteric spasm.

## **1.8. Administration of NSAIDs**

It has been shown previously that diclofenac has morphine sparing effects following major surgery. However, the major factors that impede recovery and discharge from hospital are adverse problems such as sedation, and PONV. Thus, in one RCT of this thesis, we have assessed how the morphine sparing effects of diclofenac may benefit patients after TAH.

An alternative NSAID is parecoxib, a selective COX-2 inhibitor. This is a new drug and is administered intravenously. In another RCT, we have quantified the morphine sparing effect of parecoxib after TAH and have assessed whether it is associated with reduction in patient morbidity.

# Chapter 2

## Methodology

The investigations in this thesis were all prospective double blind RCTs. All investigations were submitted to the local research Ethics Committee in Leicester for approval and patient consent was obtained.

### 2.1. Patient selection

Patients were selected according to the operation for which they were consented. The surgical procedures were:

- Total abdominal hysterectomy via a Pfannenstiel incision
- Laparoscopic sterilisation
- Laparoscopic cholecystectomy

Patients who had a history of chronic pain or who were receiving regular analgesics were excluded. Patients with severe coexisting disease or who were unable to speak English were not invited to participate.

## **2.2. Allocation of treatment**

Patients were allocated randomly to treatment, using numbers generated by computer. The instructions for providing treatment to the patient were presented to the clinician in a sealed, numbered opaque envelope. Assessors and patients were blinded to the treatment.

As measurements were repeated at various intervals in the postoperative period, a new sheet of paper with a new VAS was used on each occasion. Patients were not allowed to view previous recordings as this has been shown to influence the results (Carlsson 1983).

### **2.3.2. Analgesic consumption**

In three studies, patients received morphine by Patient Controlled Analgesia (Baxter AP II, Illinois, USA). This device recorded hourly morphine consumption and cumulative morphine consumption over 24 h was obtained from these data.

In other studies in which PCA morphine was not required, time to first rescue analgesia was recorded.

### 2.3.3. Adverse Effects

The two main adverse effects in the postoperative period were PONV and sedation.

#### PONV

Nausea was assessed on a VAS, similar to that for pain.

**Nausea**

None \_\_\_\_\_ Worst ever

When this nausea scale was used, the number of episodes of vomiting was recorded.

In two studies, however, nausea and vomiting were assessed together, using a simple categorical scale. This scale has been described in the Methods section of the individual studies.

## **Sedation**

Sedation was assessed on a VAS shown below.

Wide awake \_\_\_\_\_ Very drowsy

Patients were asked to indicate on the VAS how sleepy they were. On the rare occasion that a patient was too sleepy to produce a meaningful response, the assessor would place a mark on the far right side of the line, at “very drowsy”.

Sedation was also assessed on a 4-point ordinal scale in two of the studies. For brevity, this scale is described in the Methods section of the individual studies.

## **2.4. Statistical analysis**

### **Power calculations**

Prior to each study, a power calculation was performed on an 80% to 90% probability of detecting a predefined difference in outcome at the 5% significance level. The power calculation was based on previous published data or pilot data from our department.

In the study assessing the analgesic effects of incisional and intraperitoneal bupivacaine and epinephrine in patients having TAH, I did a power calculation based on a mean (SD) morphine consumption of 56 mg (Klein 2000).

The calculation is shown below (Table 2.1.)

**Table 2.1. Power calculation for the analgesic effects of intraperitoneal and incisional bupivacaine with epinephrine following TAH.**

Mean 24 h morphine consumption (baseline)	56 mg
Mean 24 h morphine consumption (after treatment)	36 mg
Difference in 24 h morphine consumption	20 mg
Common SD	23 mg
Size (significance level)	0.05
Power	0.8
Tails	2
Z beta	0.84
Z alpha	1.96
Sample size in each arm	22

In the study investigating the analgesic effects of intraperitoneal levobupivacaine with epinephrine following laparoscopic cholecystectomy, I did a power calculation based on pilot data in ten patients who received rescue morphine in PACU to keep their pain scores < 35 mm. For this technique to be recommended highly in patients having laparoscopic cholecystectomy on a day case basis, it would be desirable if rescue morphine consumption is 0 mg after treatment. However, instead of going for 100% reduction in rescue morphine consumption, I did the power calculation based on a more conservative decrease ie 75% (Table 2.2.).

**Table 2.2. Power calculation for the study showing whether intraperitoneal levobupivacaine with epinephrine is useful for analgesia following laparoscopic cholecystectomy.**

Mean rescue morphine consumption (baseline)	8 mg
Mean rescue morphine consumption (after treatment)	2 mg
Difference in rescue morphine consumption	6 mg
Common SD	6.6 mg
Size (significance level)	0.05
Power	0.8
Tails	2
Z beta	0.84
Z alpha	1.06
Sample size in each arm	20

The calculation of power for the study evaluating the effect of transcervical bupivacaine and papaverine in patients having laparoscopic sterilisation was based on data from Ezech (Ezech 2000). Many patients who have laparoscopic sterilisation require moderate analgesics eg cocodamol 30/500 rather than morphine. Thus, the basis for the power calculation was the proportion of patients who needed rescue analgesia rather than morphine consumption.

From Lehr's formula (Petrie 2000), the calculation is displayed below (Table 2.3.).

**Table 2.3. Power calculation for the study evaluating transcervical administration of bupivacaine for spasmodic pain after laparoscopic sterilisation: a comparison with papaverine and saline.**

Difference in proportion requiring rescue analgesia i.e. $p_1 - p_2$	0.4
$p = (p_1 + p_2) / 2$	0.8
$1 - p$	0.2
Square root $p(1 - p)$	0.4
Standardised difference squared	1
Number in each group for 80% power is $16 / \text{standardised difference}^2$	16
Number in each group for 90% power is $21 / \text{standardised difference}^2$	21

In the study assessing whether rectal diclofenac is associated with a significant reduction in opioid related side effects, I did a power calculation based on a 50% decrease in 24 h morphine consumption. The rationale for using 50% was that lower reductions in 24 h morphine eg 30% have not been associated with less nausea and sedation. Data were obtained from another study of NSAIDs in patients having TAH (Thompson 2000). The calculation is shown in Table 2.4.

**Table 2.4. Power calculation for the RCT showing whether the opioid sparing effect of rectal diclofenac benefits the patient following TAH.**

Mean 24h morphine consumption (baseline)	38 mg
Mean 24h morphine consumption (after treatment)	19 mg
Difference in 24 h morphine consumption	19 mg
Common SD	19
Size (significance level)	0.05
Power	0.8
Tails	2
Z beta	0.84
Z alpha	1.96
Sample size in each arm	16

In patients receiving parecoxib 40 mg iv for TAH, I did the power calculation based on data obtained from a similar group of patients who had parecoxib (Tang 2000). The power of the study was calculated to obtain a 35% reduction in mean 24 h morphine consumption. Components of the calculation are shown below (Table 2.5.).

**Table 2.5. Power calculation for the RCT evaluating whether the opioid sparing effect of iv parecoxib benefits the patient following TAH.**

Mean 24 h morphine consumption (baseline)	51 mg
Mean 24 morphine consumption (after treatment)	33 mg
Difference in 24 h morphine consumption	18 mg
Common SD	21 mg
Size (significance level)	0.05
Power	0.8
Tails	2
Z beta	0.84
Z alpha	1.96
Sample size in each treatment group	21

## **Processing of data and analysis**

Data were collected and tabulated in an Excel database. They analysed using Prism and SPSS for Windows. Data were analysed for normality using the Kolmogorov-Smirnov test. Appropriate parametric tests eg Student t test, one way Analysis of Variance, and non-parametric tests eg Mann Whitney U test, Chi Squared test, Kruskal Wallis test were applied.

In addition, I used the repeated measures analysis of variance to test repeated observations. After consultation with a statistician and reference to Practical Statistics for Medical Research (Altman 1991), I have made the assumption that “there is no requirement for data to be normally distributed, neither over all nor within a row or column”.

The Kaplan-Meier survival test was used for time to first analgesia in the study evaluating the analgesic effects of transcervical bupivacaine and papavarine. The log rank test was used to test for significance. In the other studies, this method of analysis was not used because of the method of administration of postoperative analgesia. Analgesia was not given at patients' request but administered by the patients via the PCA device, in three studies. In addition, in the study investigating the analgesic effects of intraperitoneal levobupivacaine with epinephrine, morphine was given in PACU to obtain a pain score of  $<35$  mm.

## **2.5. The Visual Analogue Score**

### **2.5.1. Advantages**

The VAS is a well established tool for measuring pain intensity (Price 1983). It has been shown to be valid by correlation with numerical rating (DeLoach 1998), audiometric, verbal and McGill pain assessments (McCormack 1988). In addition, the VAS is sensitive and has the capacity to detect changes in pain intensity associated with administration of analgesics (Joyce 1975, Price 1986). In a study of patients with low back pain comparing the VAS to the McGill Pain Questionnaire (MPQ), the larger area under the receiver operator curve of the VAS has demonstrated its higher sensitivity compared with the MPQ (Scrimshaw 2001).

In addition, the VAS is considered to be reliable. From a test-retest study of pain at childbirth, there was a high correlation between repeated scores when patients were asked to repeat their assessment of pain intensity (Revill 1976). Similar results have been found in patients with rheumatic pain (Joos 1991) and low back problems (Staes 2000). In the postoperative period, it was shown by Bland-Altman repeatability plots that the repeatability coefficients over three assessment periods were 13.5 mm to 23.0 mm (DeLoach 1998). Thus, it appears that the VAS has an accuracy of approximately  $\pm 20$  mm after general anaesthesia.

In the postoperative period, it has been found that the VAS is simple to understand and that it may be used easily for repeated measures. Owing to the absence of subcategories, the VAS is more sensitive than traditional descriptive pain scales for detecting changes in pain intensity (Sriwatanakul 1983).

### **2.5.2. Other types of VAS**

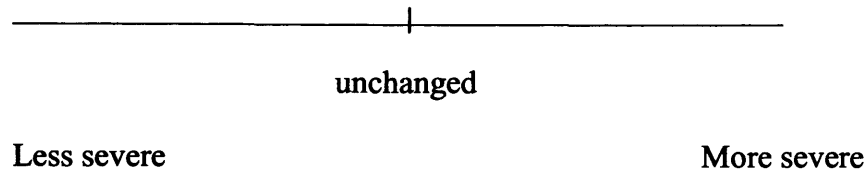
The VAS used in the studies described in this thesis is one type of VAS. Other types include different designs of line, scale, phrases and methods of recording data.

#### **Different designs of line**

A horizontal line with regular marker points, a vertical line and a curvi-linear line with and without regular marker points are variations of the plain horizontal line. In an investigation of these scales, it was shown that data recorded from the vertical scale were least normally distributed in addition to possessing the highest moment coefficients of skewness and kurtosis (Sriwatanakul 1983).

#### **Different scale**

A comparative VAS has been developed to measure relative changes in pain intensity. Marks to the left of centre represent less severe pain, and those to the right represent more severe pain intensity.



The comparative VAS is influenced by patients' expectancy over time and deficiency in memory. In patients with chronic pain, Carlsson showed that the comparative VAS was less reliable than the absolute VAS (Carlsson 1983). Thus, in the postoperative period when there is cognitive impairment, the comparative VAS would not be expected to as accurate as the absolute VAS.

**Different phrases.** (Sriwantanakul 1982)

Phrases that may be used to define the highest pain intensity include:

- Worst pain I have ever experienced
- The worst pain I have ever felt
- Pain as bad as it could be
- The worst pain I could imagine
- Severe pain
- Agonizing pain.

All these phrases are easy to understand and all have been used at one extremity of the VAS line. In practice it seems that there is no reason for choosing one phrase in preference to another.

## **Methods of recording the data from the VAS**

Pain intensity may be recorded and scored in many ways; in the studies described in this thesis, a ruler was used to measure the marks on our paper records. Alternatively, other methods may be used. The initial electronic patient information controller (EPIC), called EPIC VAS, consists of a horizontal line of 100 mm with labels of “no pain” on the left to “worst pain imaginable” on the right. Patients move the slider to a position on the line that represents their pain intensity. The slider is placed at the far left position (zero pain) prior to taking each reading. A modification of this version is the EPIC Slider that has an electronic display giving patients instructions on how to record their pain intensity (Watt 2002).

One possible criticism of the electronic slider is that it does not fully mimic how patients record data with a pen and paper. To address this limitation, an alternative electronic device termed the EPIC Glide has been developed. This consists of a similar horizontal line of 100 mm and patients are invited to use an electronic pen to indicate their pain intensity. EPIC Glide has been validated against the standard pen and paper method using a Bland-Altman analysis (Anderson 2002).

Another modification of the VAS is the visual analogue thermometer (VAT). A strip is moved to show a red band, the length of which corresponds to the magnitude of pain on a 100 mm scale (Choiniere 1996). VAT has been shown to be as sensitive as the VAS for detecting pain intensity and was preferred to the VAS in one study that enrolled healthy volunteers (Choiniere 1996).

## **2.6. Other scales for measurement of pain intensity**

### **2.6.1. Verbal rating scales**

Four point and five point verbal rating scales (VRS) may be used to quantify pain intensity (Jensen 1986). On the four point VRS, the categories are: no pain, some pain, considerable pain and pain which could not be more severe. On the five point VRS, pain may be described as mild, discomforting, distressing, horrible and excruciating. It has been shown that there is a highly significant correlation between VRS and VAS (Ohnhaus 1975). However, compared with the VRS that may artificially augment measurement of analgesic effects, the VAS appears to be a more accurate and discriminating measure of pain intensity.

### **2.6.2. Behavioural rating scale**

The behavioural rating scale (BRS) is another scale that has been used to quantify pain intensity. Patients are asked to grade their pain intensity on a six point scale. This scale ranges from: no pain; pain present, can easily be ignored; pain present, cannot be ignored, but does not interfere with everyday activities; pain present, cannot be ignored, interferes with concentration; pain present, cannot be ignored, interferes with all tasks except taking care of basic needs such as toileting and eating; and pain present, cannot be ignored, rest or bed rest required. Although the BRS has a limited

number of categories, it is useful because it may be administered either in written or verbal forms. It has been shown to have similar correct responses and predictive validity to the VAS (Jensen 1986)

### **2.6.3. Numerical rating scales**

Two numerical rating scales (NRS) have been used to measure pain intensity. They are 101 and 11 point scales, indicating “no pain” at 0, and “pain as bad as it could be” at 101 and 11, respectively. Compared with the VAS that patients need to see and mark, the NRS may be considered to be an advantage because it may be administered verbally (Jensen 1986).

For clinicians who are concerned over insufficient response categories of NRS-11, the NRS-101 has virtually an unlimited number of responses. NRS have been shown to have similar correct responses and predictive validity to the VAS (Jensen 1986)

#### **2.6.4. Categorical electronic scales**

Categorical electronic scales termed EPIC 1 and EPIC Touch have been developed in a fashion similar to the linear analogue scale, EPIC VAS (described above). These categorical scales have four buttons representing categories of pain intensity from none to severe. The difference is that EPIC 1 has buttons for the patient to press, whereas EPIC Touch has a touch sensitive keyboard with no real buttons to depress.

## **2.7. Disadvantages of the VAS**

In using the VAS, it is assumed that patients are able to transform a complex, subjective experience into a visual spatial display. In the postoperative period, there is also potential for inaccuracies owing to impaired cognitive function and vision. Furthermore, there has been concern that patients mark the VAS in clusters: at the midpoint and extremes of scale. This behaviour creates the potential for a trimodal distribution of data (Hornblow 1976) and suggests that the VAS is not associated with the capacity to detect pain intensity on a continuum. Thus, it could be argued that the VAS is only able to distinguish between pain that is mild, moderate or severe. But in practice, the VAS appears to be more sensitive than this.

The International Association for the Study of Pain has defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Thus, whilst measurement of pain intensity is appropriate for the postoperative period when cognitive function is impaired, it may not be sufficient at other times when patients are alert and not recovering from the effects of general anaesthetic drugs. In his textbook of pain, Melzack has said that, where possible, we should assess other aspects of pain (Melzack 2000). He states that, “to describe pain solely in terms of intensity or affect is like specifying the visual world only in terms of light flux without regard to pattern, colour, texture and other dimensions of visual experience”.

In 1971, Melzack and Torgerson (Melzack 1971) began the development of what has become known, in 1975, as the McGill Pain Questionnaire (MPQ) (Melzack 1975).

The main components of this questionnaire were defined under three major categories comprising words that describe the sensory, affective and evaluative components of pain. Following further evaluation, a fourth “miscellaneous” section was added. The components of the MPQ are listed below.

*Sensory category*

Temporal: flickering, quivering, pulsing, throbbing, beating, pounding.

Spatial: jumping, flashing, shooting.

Punctate pressure: pricking, boring, drilling, stabbing, lancing.

Incisive pressure: sharp, cutting, lacerating.

Constrictive pressure: pinching, pressing, gnawing, cramping, crushing.

Traction pressure: tugging, pulling, wrenching.

Thermal: hot, burning, scalding, searing.

Brightness: tingling, itchy, smarting, stinging.

Dullness: dull, sore, hurting, aching, heavy.

Sensory miscellaneous: tender, taut, rasping, splitting.

*Affective category*

Tension: tiring, exhausting.

Autonomic: sickening, suffocating.

Fear: fearful, frightful, terrifying.

**Punishment:** punishing, gruelling, cruel, vicious, killing.

**Affective miscellaneous:** wretched, blinding.

### *Evaluative*

**Present pain intensity (1-5 scale):** mild, discomforting, distressing, horrible, excruciating.

**Annoying, troublesome, miserable, intense, unbearable.**

### *Miscellaneous*

**Spreading, radiating, penetrating, piercing.**

**Tight, numb, dreading, squeezing, tearing.**

**Cool, cold, freezing.**

**Nagging, nauseating, agonising, dreadful, torturing.**

The MPQ is a well established tool for measuring pain, particularly in patients with chronic pain. It has been used extensively and has been translated into Arabic, Chinese, Czech, Danish, Dutch, Finnish, French, German, Italian, Japanese, Norwegian, Polish, Portuguese, Slovak, Spanish and Swedish. In studies over the past 30 years, it has been found to be reliable, valid, sensitive and discriminative.

Despite these advantages, this long form MPQ (LF-MPQ) has been too extensive to use in situations when time was limited to assess patients. So, an abridged version of the MPQ termed the short-form (SF-MPQ) was developed (Melzack 1975). It consists of 11 sensory and 4 affective dimensions, ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. The present pain intensity scale of no pain, mild pain, discomforting, distressing, horrible and excruciating; and the visual analogue scale of no pain to worst possible pain, were included.

In summary, the MPQ is well established: it provides the researcher with a comprehensive tool to assess all aspects of patients' pain. However, in the postoperative period when patients are recovering from the effects of general anaesthesia and cognitive function is impaired, this method of measurement is not feasible. In these circumstances, simpler scales such the VAS, VRS, NRS and BRS are more appropriate and useful.

## **Chapter 3**

### **Administration of local anaesthetics**

#### **Major abdominal surgery**

#### **3.1. The analgesic effects of intraperitoneal and incisional bupivacaine with epinephrine following TAH**

##### **3.1.1. Introduction**

At our institution, morphine administered via a PCA device is the current standard for the provision of postoperative analgesia following TAH. Patients usually require PCA for at least 24 h after which they receive oral analgesic drugs. Although PCA morphine provides satisfactory analgesia, it is associated with adverse effects such as sedation, nausea and vomiting (Stanley 1996, Woodhouse 1998). Thus, other methods of analgesia that have morphine-sparing effects are used frequently to reduce postoperative morbidity.

In clinical trials of patients undergoing TAH, administration of bupivacaine into the abdominal wall (Klein 2000)(Leung 2000)(Cobby 1997) or the peritoneal cavity (Ali 1998) during surgery has not been found to result in reduced postoperative morphine consumption compared with placebo. While intraperitoneal local anaesthetics may block afferent nociceptive transmission from visceral structures, they do not block conduction from cutaneous sites. Similarly, incisional local anaesthetics may block

nociceptive conduction from cutaneous sites but would not be expected to block conduction from visceral areas of surgery. Consequently, the failure to demonstrate beneficial effects following either incisional or intraperitoneal administration of local anaesthetic during TAH may be attributable to the hypothesis that nociceptive transmission needs to be blocked from both cutaneous and visceral sites. The objective of the present investigation was to see if administration of local anaesthetics into both visceral and cutaneous areas of surgery produces measurable analgesia following TAH.

### **3.1.2. Methods**

After obtaining local institutional Research Ethics Committee approval and informed patient consent, I studied 46 ASA I-II patients, aged 20 to 65 years, undergoing TAH. All patients received a patient information sheet and their GP was informed of their participation in the study. Postoperative assessments, for instance, the pain VAS was discussed with the patients. Theatre staff, including the anaesthetist, the Operating Department Practitioner, scrub nurse and surgeon were informed of the study. Members of the Acute Pain Service in addition to staff in the PACU and on the ward were advised that they could contact the investigators at any time via the hospital's switchboard.

Patients were excluded if TAH was scheduled for malignancy, or if there was a history of chronic pain, continuous use of analgesic drugs or inability to use the PCA device. Patients with severe cardiorespiratory or neurological disease were not invited to take part.

The anaesthetists were requested to provide all patients with a standardised anaesthetic technique comprising propofol 2-4 mg kg<sup>-1</sup>, a non-depolarising muscle relaxant and ondansetron 4 mg iv, at induction. Patients' lungs were ventilated with nitrous oxide and isoflurane 1-1.5% in oxygen, via a cuffed tracheal tube. At the end of the procedure, residual neuromuscular blockade was antagonised with a mixture of neostigmine 2.5 mg and glycopyrrolate 500 µg.

Morphine 10 mg iv was administered for intraoperative analgesia. For postoperative analgesia, patients received iv morphine by PCA, and rectal paracetamol 1 g, immediately after induction and subsequently at 6 h intervals.

Patients were allocated randomly to receive either bupivacaine 0.25% 50 ml with epinephrine 5  $\mu\text{g ml}^{-1}$  (Bupivacaine group) or 50 ml of normal saline (Placebo group), from instructions in sealed opaque numbered envelopes. Instructions inside the envelope could not be seen by holding them up to light. The randomisation was done in blocks of 6 as shown in Table 3.1. Excel and its random number generation facility were used to perform this procedure.

Bupivacaine or normal saline was drawn up in a sterile syringe by a person who was not involved further in the study. Epinephrine of concentration 1:1000 was added from a sterile 1 ml syringe. To maintain sterility, this mixture of either bupivacaine or normal saline with epinephrine was dispensed into a Gallipot so that the scrub nurse could draw it up for the surgeon to administer.

Prior to wound closure, 30 ml and 20 ml of the appropriate treatment solution were administered into the peritoneal cavity and abdominal wall respectively. The surgeon who was blinded to the treatment was asked to infiltrate all layers of the abdominal wall during closure, including muscle and cutaneous layers.

In the postoperative period, assessments were made on awakening and then at 8 h, 12 h, and at 24 h, by a trained nurse or doctor blinded to the treatment. Pain at rest and on movement (induced by sitting) was assessed on a 100 mm VAS. Sedation was

assessed using a categorical scale of 0 for patient alert; 1 for occasionally drowsy but easy to arouse; 2 for frequently drowsy but easy to arouse; 3 for severely drowsy and difficult to arouse; and 4 for normal sleep. In addition, PONV were assessed on a categorical scale comprising 0 for none, 1 for nausea, 2 for vomiting on one occasion, and 3 for vomiting on more than one occasion. Morphine consumption was recorded by the PCA device.

Full details of the power calculation were presented earlier in the chapter on Methodology. From a previous study on incisional infiltration of bupivacaine with epinephrine in our department (Klein 2000), we considered that to have an 80% chance of detecting a 35% reduction in 24h morphine consumption at the 5% significance level, 22 patients per group would be required.

Data were processed in Excel 2000 and SPSS 9.5. I used a number of statistical tests to analyse the data collected in this study. Data were assessed for normality using the Kolmogorov Smirnov test and appropriate parametric and non-parametric test were used to test for significance.  $P < 0.05$  was considered to be statistically significant. If data were parametric, then I have expressed them as mean (95% CI). If data were non-parametric, then I have expressed them as median (interquartile range).

Age and weight were expressed as mean (95% CI) and analysed by the unpaired two-tailed Student t test. Duration of surgery was expressed as median (interquartile range) and analysed by the Mann Whitney U test. ASA status was analysed using the chi-squared test.

To take into account the fact that some pain scores were not normally distributed, I have expressed them as median (interquartile range). Pain at rest and on movement were repeated observations and so I have analysed them by analysis of variance for repeated measures.

24 h morphine consumption was not normally distributed, and so I have expressed it as median (interquartile range). To test for significance, the Mann Whitney U test was used. In addition, to explain the difference in morphine consumption in the postoperative period, hourly morphine consumption was assessed. Differences in 24 h morphine consumption was tested, in this case, by analysis of variance for repeated measures and Bonferroni correction was used for multiple comparisons.

Similarly, sedation and nausea were repeated observations in the postoperative period. They have been expressed as median (interquartile range) and analysed by analysis of variance for repeated measures.

### **3.1.3. Results**

Of 46 patients, 13 did not complete the study for the following reasons: PCA malfunction, PCA discontinued too early, nausea, chest infection, intra-abdominal drain insertion and protocol violation (Table 3.2).

There were no significant differences in age, weight or duration of surgery between the remaining patients (Table 3.3.). However, in the bupivacaine group, there were significantly ( $P=0.03$ ) more ASA I and fewer ASA II patients than in the placebo group.

Median (interquartile range) morphine consumption was significantly ( $P<0.01$ ) smaller in the bupivacaine group [44(32 to 56) mg] than in the placebo group [62(53 to 85) mg] (Fig 3.1.). This significant difference was attributable largely to the reduction in morphine consumption within the first 4 h postoperatively (Fig 3.2.).

On awakening, pain scores on movement, but not at rest, were significantly ( $P=0.01$ ) less in the bupivacaine group than in the placebo group. At 8 h, 12 h and 24 h, however, there was no difference in pain scores between the two groups (Table 3.4.).

With the exception of the low median (interquartile range) sedation score of 1(0-2) in the bupivacaine group and 0(0-0) in the placebo group at 24 h, there were no significant differences between the groups in sedation and nausea (Table 3.5.).

### 3.1.4. Tables

**Table 3.1 Randomisation of treatment**

Patient no	Block no	Random no	Treatment
1	1	3.1	Bupivacaine
2	1	4.6	Placebo
3	1	1.1	Bupivacaine
4	1	1.1	Bupivacaine
5	1	4.9	Placebo
6	1	4.1	Placebo
7	1	3.7	Placebo
8	1	8.0	Bupivacaine
9	2	1.9	Bupivacaine
10	2	6.4	Placebo
11	2	3.4	Bupivacaine
12	2	5.1	Placebo
13	2	6.3	Placebo
14	2	1.4	Bupivacaine
15	2	6.7	Bupivacaine

**Table 3.1      Randomisation of treatment**

<b>Patient no</b>	<b>Block no</b>	<b>Random no</b>	<b>Treatment</b>
16	2	3.2	Placebo
17	3	6.5	Bupivacaine
18	3	4.3	Bupivacaine
19	3	5.1	Bupivacaine
20	3	1.3	Bupivacaine
21	3	5.0	Placebo
22	3	5.9	Placebo
23	3	5.9	Placebo
24	3	6.8	Placebo
25	4	6.4	Placebo
26	4	6.2	Bupivacaine
27	4	6.8	Bupivacaine
28	4	3.9	Placebo
29	4	6.3	Placebo
30	4	1.9	Bupivacaine

**Table 3.1      Randomisation of treatment**

<b>Patient no</b>	<b>Block no</b>	<b>Random no</b>	<b>Treatment</b>
31	4	4.3	Bupivacaine
32	4	1.4	Placebo
33	5	2.7	Bupivacaine
34	5	6.0	Bupivacaine
35	5	3.6	Bupivacaine
36	5	3.6	Placebo
37	5	4.8	Bupivacaine
38	5	6.9	Placebo
39	5	1.1	Placebo
40	5	4.5	Placebo
41	6	0.993817	Placebo
42	6	0.496969	Bupivacaine
43	6	0.552865	Bupivacaine
44	6	0.126587	Placebo
45	6	0.641678	Bupivacaine
46	6	0.423662	Placebo
47	6	0.941801	Bupivacaine
48	6	0.487154	Placebo

**Table 3.2      Reasons for patient withdrawal**

	<b>Placebo</b>	<b>Bupivacaine</b>
<b>Pump malfunction or discontinued early</b>	3	0
<b>Nausea requesting withdrawal</b>	1	1
<b>Chest infection</b>	0	1
<b>Intra-abdominal drain insertion</b>	1	4
<b>Protocol violation</b>	1	1

Data expressed as number of patients.

**Table 3.3. Baseline characteristics**

	<b>Placebo</b> n=17	<b>Bupivacaine</b> n=16	<b>p</b>
Age (y)	42(38-46)	42(38-46)	ns
Weight (kg)	67(60-74)	66(62-70)	ns
ASA I/II	8/9	14/2	0.03
Duration of surgery (min)	65(60-77)	63(56-75)	ns

Age and weight expressed as mean (95% CI) and analysed by the unpaired two-tailed Student t test.

Duration of surgery expressed as median (interquartile range) and analysed by the Mann Whitney U test.

ASA status was analysed using the Chi Squared test.

ns: no significant difference between groups

**Table 3.4. Pain VAS**

<b>Time postoperatively (h)</b>	<b>Activity</b>	<b>Placebo (mm)</b>	<b>Bupivacaine (mm)</b>	<b>p</b>
0	Rest	70(50-80)	50(28-62)	ns
	Movement	80(68-80)	50(44-63)	0.01
8	Rest	40(27-56)	45(29-53)	ns
	Movement	75(60-80)	72(49-82)	ns
12	Rest	30(10-40)	34(9-58)	ns
	Movement	60(40-70)	50(28-79)	ns
24	Rest	22(8-50)	36(6-50)	ns
	Movement	57(22-70)	50(36-68)	ns

Data expressed as median (interquartile range).

Pain at rest and on movement were analysed by analysis of variance for repeated measures.

ns: no significant difference between groups

**Table 3.5. Adverse Effects**

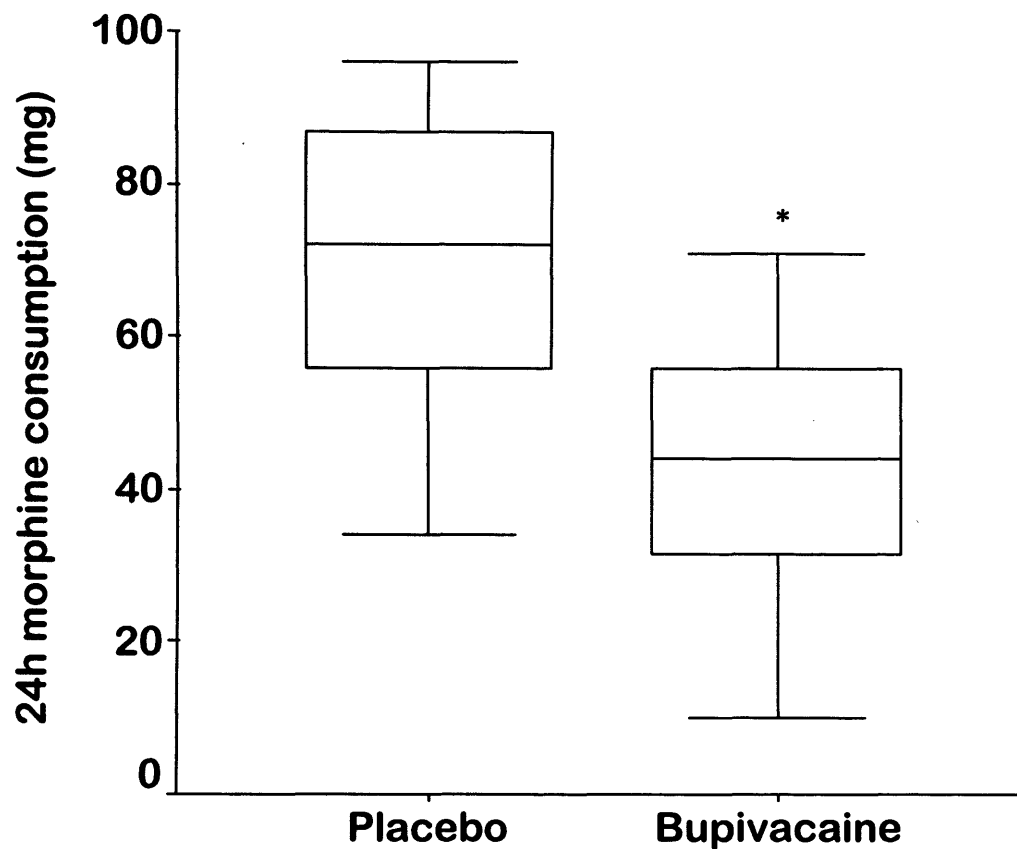
	Time postoperatively (h)	Placebo	Bupivacaine	p
<b>Sedation</b>	0	1(1-1)	1(0-2)	ns
	8	0(0-1)	1(0-2)	ns
	12	1(0-1)	0(0-2)	ns
	24	0(0-0)	1(0-2)	<0.01
<b>Nausea</b>	0	0(0-0)	0(0-0)	ns
	8	0(0-1)	0(0-1)	ns
	12	0(0-0)	0(0-1)	ns
	24	0(0-1)	0(0-1)	ns

Data expressed as median (interquartile range) and analysed by analysis of variance for repeated measures.

ns: no significant difference between groups

### 3.1.5. Figures

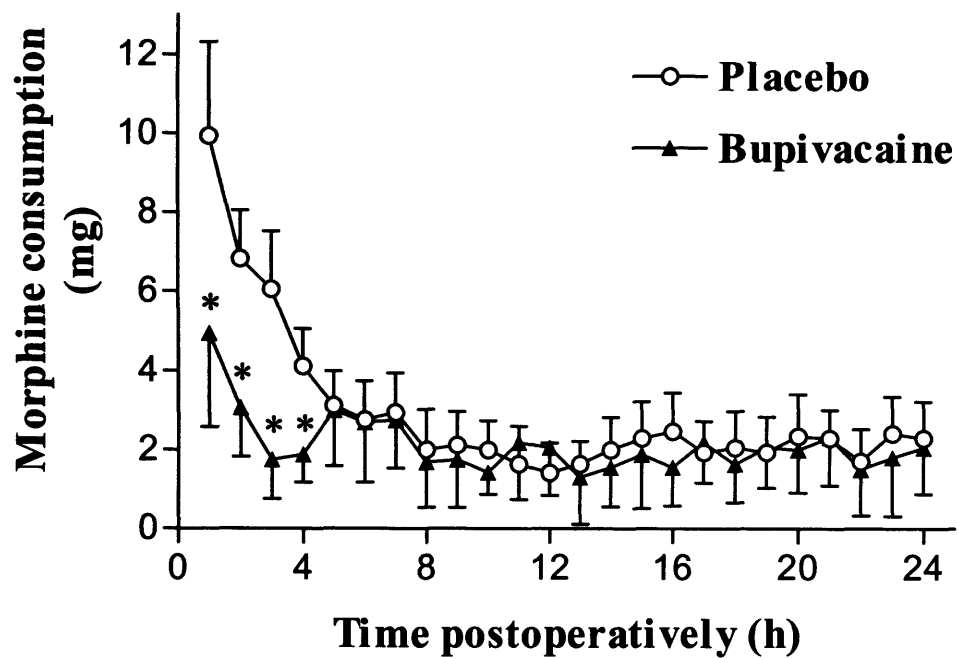
**Fig 3.1. 24h Morphine consumption**



Data expressed as median (interquartile range) with min to max limits, and analysed by Mann Whitney U test.

\* Significant difference between groups ( $P < 0.01$ )

**Fig 3.2. Hourly Morphine Consumption**



Data expressed as mean (95% CI) and analysed by analysis of variance for repeated measures.

\* Significant difference between groups ( $P < 0.01$ )

## **Minimally invasive surgery**

### **3.2. Is intraperitoneal levobupivacaine with epinephrine useful for analgesia following laparoscopic cholecystectomy?**

#### **3.2.1. Introduction**

Laparoscopic cholecystectomy in healthy patients is often performed at our hospital on a day case basis. Despite being minimally invasive, this operation may cause patients to experience severe pain that delays discharge from hospital and so strong opioid analgesia eg morphine is often prescribed. However, morphine is not an ideal analgesic for day case anaesthesia because of adverse effects such as sedation, nausea, vomiting, and delayed return of gastrointestinal motility. Other drugs that provide morphine-sparing analgesia eg non-selective NSAIDs (Ng, Parker 2002), COX-2 inhibitors (Ng, Smith, Davidson 2003) and local anaesthetic infiltration (Ng, Swami, Smith, Davidson 2002) are usually used to supplement analgesia.

Intraperitoneal instillation of local anaesthetic around the operative site has been used as an analgesic technique on the premise that it blocks conduction from visceral sites and that it may reduce the extent of referred pain to the shoulder in the postoperative period (Pasqualucci 1996, Elhakim 2000, Gharaibeh 2000). However, in previous studies of intraperitoneal local anaesthetics following laparoscopic cholecystectomy, it has not been possible to demonstrate consistently reliable analgesic effects (Ng, Smith

2002 BJA editorial) (Raetzell 1995, Scheinin 1995, Joris 1995 Elfberg 2000 Zmora 2000); this may be related to the presence of nociceptive conduction from incisional sites that is not blocked by intraperitoneal local anaesthetics. Administration of local anaesthetics into incisional sites has been shown to produce analgesia after laparoscopic cholecystectomy (Wills 2000) and therefore the object of this study in patients having laparoscopic cholecystectomy was to evaluate if intraperitoneal instillation of levobupivacaine with epinephrine provides analgesia for visceral and shoulder pain, in the presence of incisional local anaesthetic.

### 3.2.2. Methods

After obtaining local research Ethics Committee approval and informed patient consent, I studied 48 ASA I to II patients scheduled for laparoscopic cholecystectomy. All patients were given a patient information sheet and their General Practitioner was informed that they were participants. Patients were advised that that they were to receive suppositories of analgesia at induction of general anaesthesia. Postoperative measurements were explained to the patient. In particular, the three locations of pain ie in the abdomen, the shoulder and in the abdominal wall were discussed.

Patients who had a chronic pain syndrome or who used analgesics regularly were excluded. In addition, any patient who had pain, for instance, from biliary colic, was not eligible for this study. Patients sensitive to drugs eg diclofenac in the trial protocol were not invited to participate.

All patients were given a standardised anaesthetic comprising propofol 2-4 mg kg<sup>-1</sup>, fentanyl 2 µg kg<sup>-1</sup>, ondansetron 4 mg iv and atracurium 0.5 mg kg<sup>-1</sup>. Their lungs were ventilated with nitrous oxide and isoflurane 1-1.5% in oxygen. Suppositories of diclofenac 100 mg and paracetamol 1 g were administered at induction.

On wound closure, incisional sites were infiltrated with levobupivacaine 20 ml of 2.5 mg ml<sup>-1</sup> with epinephrine 5 µg ml<sup>-1</sup>, in all patients. This solution was prepared by the anaesthetist who was not involved further in the study. Epinephrine 100 µg (0.1 ml of 1:1000) was added to a 20 ml syringe containing levobupivacaine. This mixture was

then emptied into a Gallipot for the nurse assisting the surgeon to draw up in another sterile 20 ml syringe.

At the end of surgery, residual neuromuscular blockade was antagonised with a mixture of neostigmine 2.5 mg and glycopyrrolate 500  $\mu\text{g ml}^{-1}$ .

Using instructions in a sealed opaque envelope, patients were allocated randomly by computer to receive either levobupivacaine 30 ml of 2.5  $\text{mg ml}^{-1}$  with epinephrine 5  $\mu\text{g ml}^{-1}$  or 30 ml of normal saline with epinephrine 2.5  $\text{mg ml}^{-1}$ . The solution was administered into the peritoneal cavity, to the gall bladder bed and above the liver, just before wound closure. The solution was prepared by the anaesthetist who was not involved further in the study. Epinephrine 150  $\mu\text{g}$  (0.15 ml of 1:1000) was added to a syringe containing either 30 ml of levobupivacaine 2.5  $\text{mg ml}^{-1}$  or 30 ml of normal saline. This mixture was then ejected into a Gallipot that was separate from the one used to contain the 20 ml of levobupivacaine with epinephrine 2.5  $\text{mg ml}^{-1}$ . The nurse assisting the surgeon was asked to draw up this mixture. Both this mixture and the one for incisional instillation were colourless. However, it was not possible to confuse them because they were of different volumes.

Randomisation of treatment was done on Excel using its random number generation facility. Allocation of treatment is shown in Table 3.6.

In the postoperative period, patients were assessed, on awakening and then at 1 h, 2 h, 3 h and 4 h by a doctor or nurse blinded to the drug given. Intraabdominal pain at rest and on deep inspiration, incisional pain at rest and on deep inspiration, and pain in the

right and left shoulders were assessed on a VAS. Patients were advised that incisional pain was pain in the skin that they could touch and that intraabdominal pain was deep pain that they could not touch. Nausea and sedation were assessed also on a similar VAS, representing “no nausea” and “fully awake” on the left, and “worst imaginable nausea” and “very drowsy” on the right, respectively. In the Post Anaesthetic Care Unit (PACU), morphine 2 mg iv was administered, at 5 min intervals, to ensure that intraabdominal pain at rest was < 35 mm.

For this method of analgesia to be useful in day surgery, the dose of rescue morphine should be as close to zero as possible. From pilot data, we estimated that 20 patients per treatment group were required to allow an 80% chance of detecting a 75% reduction in the dose rescue of morphine in PACU.

Data were processed in Excel 2000 and SPSS 11.0. Age, weight and height are expressed as mean (95% CI) and were analysed by the unpaired two-tailed Student t test. Duration of surgery is expressed as median (interquartile range) and was analysed by the Mann Whitney U test. ASA status was analysed by the chi-squared test.

Pain intensity in the incision, shoulder and abdomen of the first 4 h postoperatively were summed and were tested for normality using the Kolmogorov-Smirnov test. Not all of them were normally distributed and so I have expressed pain intensity as median (interquartile range). These data were analysed by the Mann Whitney U test. Similarly, sedation and nausea have been expressed as median (interquartile range) and analysed by the Mann Whitney U test.

Dose of morphine, dose of dihydrocodeine and cyclizine are expressed as median (interquartile range). The Mann Whitney U test was used for analysis of these data.

Number of patients requiring rescue analgesia ie morphine or both morphine and dihydrocodeine were analysed by the chi-squared test. This test was also used to analyses episodes of vomiting.

### 3.2.3. Results

Of 48 patients, 5 were excluded (Table 3.7). Of 43 patients studied, there were no significant differences between the two treatment groups in age, weight, height, ASA status, duration of surgery or number of patients with abdominal drains inserted (Table 3.8.).

Median (interquartile range) total abdominal pain on inspiration in the levobupivacaine group was significantly ( $p < 0.05$ ) lower [71(21-129) mm] than that in the placebo group [123(71-179) mm] (Table 3.9.). However, median (interquartile range) total abdominal pain at rest in the levobupivacaine group was not significantly ( $P = 0.08$ ) lower [72(35-128) mm] than that in the placebo group [101(76-134) mm]. In addition, median (interquartile range) total right shoulder pain of 0(0-20) mm in the levobupivacaine group did not differ significantly ( $p = 0.07$ ) from that of 16(0-49) mm in the placebo group. Of other pain scores, there were no significant differences between the two groups in total left shoulder pain, total incisional pain at rest or total incisional pain on inspiration.

The percentage of patients needing rescue morphine (38%) or morphine and dihydrocodeine (43%) in the levobupivacaine group was lower but not significantly so compared with those (of 59% and 68% respectively) in the placebo group (Table 3.10.). Median (interquartile range) total rescue morphine consumption in the levobupivacaine group was not significantly lower [0(0-7) mg] than that in the placebo group [2(0-10) mg]. Dihydrocodeine and cyclizine administration was also not significantly different between the two treatment groups. In addition, there was

no significant difference in total sedation score, total nausea score or number of episodes of vomiting between the groups (Table 3.11.).

### 3.2.4. Tables of results

**Table 3.6. Randomisation of treatment**

Patient no	No in a block	Random no	Treatment
1	1	0.047083	Saline
2	2	0.690119	Levobupivacaine
3	3	0.591641	Levobupivacaine
4	4	0.617325	Saline
5	5	0.96044	Saline
6	6	0.721295	Levobupivacaine
7	1	0.490408	Saline
8	2	0.559485	Levobupivacaine
9	3	0.734686	Levobupivacaine
10	4	0.911239	Levobupivacaine
11	5	0.505898	Saline
12	6	0.637528	Saline
13	1	0.172817	Levobupivacaine
14	2	0.452719	Saline
15	3	0.622263	Saline

**Table 3.6. Randomisation of treatment**

<b>Patient no</b>	<b>No in a block</b>	<b>Random no</b>	<b>Treatment</b>
16	4	0.37114	Levobupivacaine
17	5	0.360494	Saline
18	6	0.450301	Levobupivacaine
19	1	0.223044	Levobupivacaine
20	2	0.941593	Saline
21	3	0.595532	Saline
22	4	0.619796	Levobupivacaine
23	5	0.926753	Saline
24	6	0.724237	Levobupivacaine
25	1	0.995424	Saline
26	2	0.3755	Saline
27	3	0.554034	Levobupivacaine
28	4	0.484201	Levobupivacaine
29	5	0.269835	Saline
30	6	0.851876	Levobupivacaine

**Table 3.6. Randomisation of treatment**

<b>Patient no</b>	<b>No in a block</b>	<b>Random no</b>	<b>Treatment</b>
31	1	0.795959	Levobupivacaine
32	2	0.257263	Levobupivacaine
33	3	0.217378	Saline
34	4	0.161291	Saline
35	5	0.253132	Saline
36	6	0.327966	Levobupivacaine
37	1	0.188751	Saline
38	2	0.282148	Saline
39	3	0.574932	Levobupivacaine
40	4	0.085568	Levobupivacaine
41	5	0.619191	Levobupivacaine
42	6	0.933334	Saline
43	1	0.985667	Saline
44	2	0.446605	Levobupivacaine
45	3	0.319092	Levobupivacaine
46	4	0.014104	Saline
47	5	0.483885	Levobupivacaine
48	6	0.72414	Saline

**Table 3.7. Patients excluded**

<b>Placebo</b>	<b>n</b>	<b>Levobupivacaine</b>	<b>n</b>
Intraperitoneal solution not administered	1	Protocol violation	1
Patient declined to take part further in the study	1	Haemorrhage precluding a standard surgical technique	1

Data expressed as number of patients.

**Table 3.8. Baseline characteristics**

	<b>Placebo</b> n=22	<b>Levobupivacaine</b> n=21
Age (y)	48(41-55)	44(39-49)
Weight (kg)	72(66-78)	78(71-86)
Height (cm)	163(159-167)	167(162-171)
ASA status I/II	11/11	10/11
Duration of surgery (min)	48(39-90)	55(45-60)
No of patients without/ with abdominal drain	10/11	13/8

Age, weight and height are expressed as mean (95% CI) and were analysed by the unpaired two-tailed Student t test.

Duration of surgery is expressed as median (interquartile range) and was analysed by the Mann Whitney U test.

ASA status was analysed by the chi-squared test.

No significant difference between placebo and levobupivacaine groups

**Table 3.9. Pain intensity scores**

	<b>Placebo</b>	<b>Levobupivacaine</b>	<b>p</b>
Abdominal pain at rest (mm)	101(76-134)	72(35-128)	0.08
Abdominal pain on inspiration (mm)	123(71-179)	71(21-129)	0.04
Right shoulder pain (mm)	16(0-49)	0(0-20)	0.07
Left shoulder pain (mm)	1(0-4)	0(0-10)	ns
Incisional pain at rest (mm)	69(32-95)	44(14-80)	ns
Incisional pain on inspiration (mm)	92(39-130)	37(21-103)	ns

Pain scores in patients given either 30 ml of levobupivacaine 2.5 mg ml<sup>-1</sup> with epinephrine 5 µg ml<sup>-1</sup> or placebo following laparoscopic cholecystectomy.

Data are expressed as median (interquartile range) and were analysed on SPSS using the Mann Whitney U test.

Statistical significance when  $P < 0.05$

**Table 3.10. Drug consumption**

	<b>Placebo</b>	<b>Levobupivacaine</b>	<b>p</b>
<b>Morphine (mg)</b>	2(0-10)	0(0-7)	ns
<b>Dihydrocodeine (mg)</b>	0(0-0)	0(0-15)	ns
<b>Patients needing morphine (%)</b>	59	38	ns
<b>Patients needing morphine and dihydrocodeine (%)</b>	68	43	ns
<b>Cyclizine (no of patients)</b>	0(0-1)	0(0-1)	ns

Dose of morphine, dose of dihydrocodeine and cyclizine are expressed as median (interquartile range). They were analysed on SPSS using the Mann Whitney U test.

Number of patients requiring rescue analgesia ie morphine or both morphine and dihydrocodeine were analysed by the chi-squared test.

ns: non significant

**Table 3.11. Adverse effects**

	<b>Placebo</b>	<b>Levobupivacaine</b>	<b>p</b>
<b>Sedation (mm)</b>	118(69-209)	102(52-188)	ns
<b>Nausea (mm)</b>	23(7-64)	16(2-66)	ns
<b>Vomiting (no of episodes)</b>	0(0-0)	0(0-0)	ns

Sedation and nausea are expressed as median (interquartile range). They were analysed by the Mann Whitney U test.

Number of vomiting episodes were analysed using the chi-squared test.

ns: not significant

### **3.3. Transcervical administration of bupivacaine for spasmodic pain after laparoscopic sterilisation: a comparison with papaverine and saline**

#### **3.3.1. Introduction**

A critical factor that delays discharge and leads to hospital admission is pain after day case surgery (Audit Commission 1997). Laparoscopic sterilisation is a common procedure and in comparison with diagnostic gynaecological laparoscopy, it is believed that tight clips or rings applied to fallopian tubes causes additional pain (Davis 1998) induced by ischaemia or spasm (Edwards 1991). On their own, NSAIDs are not sufficiently efficacious to treat this pain and a strong opioid such as morphine is required in some patients. However, morphine is not ideal for day case anaesthesia because it is associated with increased adverse effects such as sedation, PONV and respiratory depression. Thus alternative methods such as local anaesthetic agents eg bupivacaine, and drugs with muscle relaxants properties eg papaverine, may be useful, the former in blocking neural conduction and the latter in reducing tubular spasm.

The purpose of this study was to investigate the analgesic effects of bupivacaine and papaverine, administered by the transcervical route prior to application of Filshie clips, during laparoscopic sterilisation.

### **3.3.2. Methods**

After obtaining local institutional Ethics Committee approval and informed patient consent, I studied 66 females of grades ASA 1 to II, undergoing laparoscopic sterilisation. All patients were given a patient information sheet concerning the conduct of the trial. In addition, their General Practitioner was informed of their participation. Pain assessments and the provision of postoperative rescue analgesia were explained preoperatively.

Exclusion criteria were known allergies to bupivacaine and papaverine, diagnosed chronic pain syndrome, pelvic inflammatory disease, pelvic adhesions and a history of regular analgesic ingestion. Exclusions concerning surgery were operative difficulties such as incorrect insufflation, conversion to an open procedure, use of more than one clip to one Fallopian tube and the application of the clip on the lateral two-thirds of the Fallopian tube.

All patients were given a standardised general anaesthetic comprising propofol 2-4 mg kg<sup>-1</sup>, fentanyl 1 µg kg<sup>-1</sup> and a muscle relaxant at induction of anaesthesia. Patients' lungs were ventilated to normocapnia with 66% nitrous oxide and isoflurane 1-2% in oxygen via a standard laryngeal mask airway. Suppositories of diclofenac 100 mg and ondansetron 4 mg iv were administered at the beginning of surgery. Residual neuromuscular blockade was antagonised with a mixture of neostigmine 2.5 mg and glycopyrrolate 500 µg. In the postoperative period, rescue analgesia comprised oral codeine 60 mg with oral paracetamol 1 g, and morphine 10 mg im.

Patients were allocated randomly to one of three treatment groups: bupivacaine, papaverine and placebo (Fig 3.3). These groups were determined by computerised random number generation, in blocks of six (Table 3.12).

An independent person prepared the appropriate solution from instructions in sealed randomised envelopes. The solutions comprised 30 ml of normal saline, 30 ml of bupivacaine 0.375 %, and papaverine 30 mg in 30 ml of normal saline.

Prior to application of the Filshie clips, 30 ml of the appropriate solution were injected carefully through a Spackman's cannula placed into the cervix of the uterus. The syringe was left at the end of the cannula to prevent reverse flow of drug out of the cannula. A Filshie clip was applied to the medial one-third of each Fallopian tube. Manipulation of the uterus during sterilisation was carried out using the Spackman's cannula.

Records were made of the time of drug administration and any difficulties encountered during the procedure.

In the postoperative period, visual analogue pain scores were recorded at rest on a scale of 0 mm (no pain) to 100 mm (worst ever pain). Assessments were made on awaking, 30 minutes later and then at 1, 2, 3 and 4 h postoperatively, by an observer blinded to the patient group.

Time to rescue analgesia was recorded. In addition, side effects such as hypotension, nausea and vomiting were recorded. At the same time intervals, suitability for discharge was assessed using our hospital's day surgery unit guidelines.

Details of the power calculation are in the Methodology chapter. From a previously published study (Ezech 1995) on the efficacy of local anaesthetics administered to patients undergoing laparoscopic sterilisation, it was estimated that 21 patients per group were needed for a 90% chance of detecting a 40% reduction in the proportion of patients requesting rescue analgesia within the first postoperative hour.

Data were entered into Excel and analysed using SPSS 9.5. They were tested for normality using the Kolmogorov Smirnov test. If data were normally distributed, then they were expressed as mean (95% CI). On the other hand, if data were not normally distributed, then they were expressed as median (interquartile range).

Age is expressed as mean (95% CI) and was analysed using one way analysis of variance. BMI is expressed as median (interquartile range) and was analysed using the Kruskal Wallis test. ASA status was analysed by the chi-squared test.

Pain intensity scores were not all normally distributed and so I have expressed them as median (interquartile range). These measurements were repeated and consequently I have used analysed them using analysis of variance for repeated measures.

Numbers of patients requiring rescue analgesia ie cocodamol and morphine were analysed by the chi-squared test. In addition, this test was used to test the number of patients with PONV and needing rescue anti-emetic.

Kaplan Meier Survival was used to analyse data of time to first analgesia and a Log Rank Test was used to test for statistical significance of the graphical data.

### **3.3.3. Results**

Of the 66 patients recruited, three did not complete the study. One patient in the saline group had prolonged apnoea to mivacurium requiring admission to the Intensive Care Unit. On further investigation, she was found to have plasma cholinesterase deficiency. Another patient in the same group changed her mind and declined to participate in the study. One patient in the bupivacaine group was excluded because of a retroverted uterus that did not allow transcervical administration

The three groups were similar in physical characteristics. There were no significant differences in mean age, median BMI and ASA status between the three groups (Table 3.13.).

There were no significant differences in the median VAS pain scores between the three groups at all times in the postoperative period (Table 3.14.). The time to first analgesia and median survival times did not differ significantly between the three groups (Fig 3.4., Table 3.15.).

Consumption of codeine 60 mg with paracetamol 1 g only, morphine only, or the combination of codeine 60 mg with paracetamol 1 g and morphine, did not differ significantly between the three groups (Table 3.16.). In addition, the number of patients in each group having analgesia within the first postoperative hour did not differ significantly.

The combined incidence of postoperative nausea and vomiting was 19%. There was no significant difference between the groups in PONV or requirement for additional antiemetics (Table 3.17.). Sedation scores were low and did not differ significantly between the groups. In addition, no adverse effects of bupivacaine or papaverine eg hypotension were detected.

### 3.3.4. Tables

**Table 3.12. Randomisation of treatment.**

Patient no	Block no	Treatment	Random no
1	1	Placebo	0.461519
2	1	Bupivacaine	0.700047
3	1	Placebo	0.398256
4	1	Papaverine	0.426333
5	1	Papaverine	0.516157
6	1	Bupivacaine	0.261708
7	2	Placebo	0.781392
8	2	Bupivacaine	0.712874
9	2	Placebo	0.427966
10	2	Papaverine	0.560186
11	2	Bupivacaine	0.114602
12	2	Papaverine	0.487791
13	3	Placebo	0.207348
14	3	Bupivacaine	0.558334
15	3	Placebo	0.553691

**Table 3.12. Randomisation of treatment.**

<b>Patient no</b>	<b>Block no</b>	<b>Treatment</b>	<b>Random no</b>
16	3	Papaverine	0.720032
17	3	Bupivacaine	0.016598
18	3	Papaverine	0.794442
19	4	Papaverine	0.223424
20	4	Placebo	0.226004
21	4	Bupivacaine	0.62643
22	4	Placebo	0.009667
23	4	Papaverine	0.343272
24	4	Bupivacaine	0.482133
25	5	Bupivacaine	0.785134
26	5	Placebo	0.599445
27	5	Papaverine	0.386023
28	5	Bupivacaine	0.030425
29	5	Placebo	0.442196
30	5	Papaverine	0.614151

**Table 3.12. Randomisation of treatment.**

<b>Patient no</b>	<b>Block no</b>	<b>Treatment</b>	<b>Random no</b>
31	6	Papaverine	0.300826
32	6	Bupivacaine	0.38218
33	6	Bupivacaine	0.495255
34	6	Placebo	0.060159
35	6	Papaverine	0.148164
36	6	Placebo	0.463939
37	7	Papaverine	0.324362
38	7	Bupivacaine	0.330286
39	7	Placebo	0.238376
40	7	Papaverine	0.802897
41	7	Placebo	0.999001
42	7	Bupivacaine	0.265843
43	8	Placebo	0.342408
44	8	Papaverine	0.263976
45	8	Papaverine	0.8443

**Table 3.12. Randomisation of treatment.**

<b>Patient no</b>	<b>Block no</b>	<b>Treatment</b>	<b>Random no</b>
46	8	Bupivacaine	0.017237
47	8	Placebo	0.623597
48	8	Bupivacaine	0.793102
49	9	Bupivacaine	0.948833
50	9	Bupivacaine	0.788398
51	9	Papaverine	0.078547
52	9	Placebo	0.015512
53	9	Placebo	0.576386
54	9	Papaverine	0.357918
55	10	Bupivacaine	0.896468
56	10	Placebo	0.372897
57	10	Bupivacaine	0.066752
58	10	Placebo	0.432777
59	10	Papaverine	0.768418
60	10	Papaverine	0.969351

**Table 3.12. Randomisation of treatment.**

<b>Patient no</b>	<b>Block no</b>	<b>Treatment</b>	<b>Random no</b>
61	11	Bupivacaine	0.925236
62	11	Placebo	0.575875
63	11	Bupivacaine	0.88216
64	11	Placebo	0.904275
65	11	Papaverine	0.09173
66	11	Bupivacaine	0.091204

**Table 3.13.****Baseline characteristics**

	<b>Placebo</b> n=20	<b>Bupivacaine</b> n=21	<b>Papaverine</b> n=22
Age (y)	34(30-37)	33(31-35)	35(33-37)
BMI (kg m <sup>-2</sup> )	23(22-26)	25(22-27)	26(24-28)
ASA I/II	15/5	19/2	19/3

Age is expressed as mean (95% CI) and was analysed using one way analysis of variance.

BMI is expressed as median (interquartile range) and was analysed using the Kruskal Wallis test.

ASA status was analysed by the chi-squared test.

No significant difference between groups

**Table 3.14. Visual Analogue Pain Scores (mm).**

<b>Time (h)</b>	<b>Placebo</b>	<b>Bupivacaine</b>	<b>Papaverine</b>	<b>p</b>
0	34(19-68)	35(29-47)	20(15-45)	ns
0.5	50(35-79)	66(51-70)	55(19-75)	
1	44(22-69)	60(56-70)	60(15-79)	
2	27(13-52)	35(30-45)	47(4-72)	
3	22(11-45)	17(5-35)	13(4-51)	
4	11(1-24)	12(2-24)	8(0-23)	

Data expressed as median (interquartile range)

Comparisons made using analysis of variance for repeated measures.

**Table 3.15. Time to first administration of analgesia (min)**

<b>Saline</b>	<b>Bupivacaine</b>	<b>Papaverine</b>	<b>p</b>
35(17-240)	45(20-75)	35(30-110)	ns

Data shown as median (interquartile range)]

Log rank test used to test for significance.

**Table 3.16. Analgesic Consumption**

<b>Analgesia</b>	<b>Placebo</b>	<b>Bupivacaine</b>	<b>Papaverine</b>	<b>p</b>
None	6	3	5	ns
Codeine 60mg + Paracetamol 1g	13	17	16	ns
Morphine 10 mg only	7	3	6	ns
Codeine 60 mg + Paracetamol 1 g Plus Morphine 10 mg	5	2	5	ns
Analgesia within 1 h postoperatively	13	13	15	ns

Data expressed as number of patients and analysed by the chi-squared test.

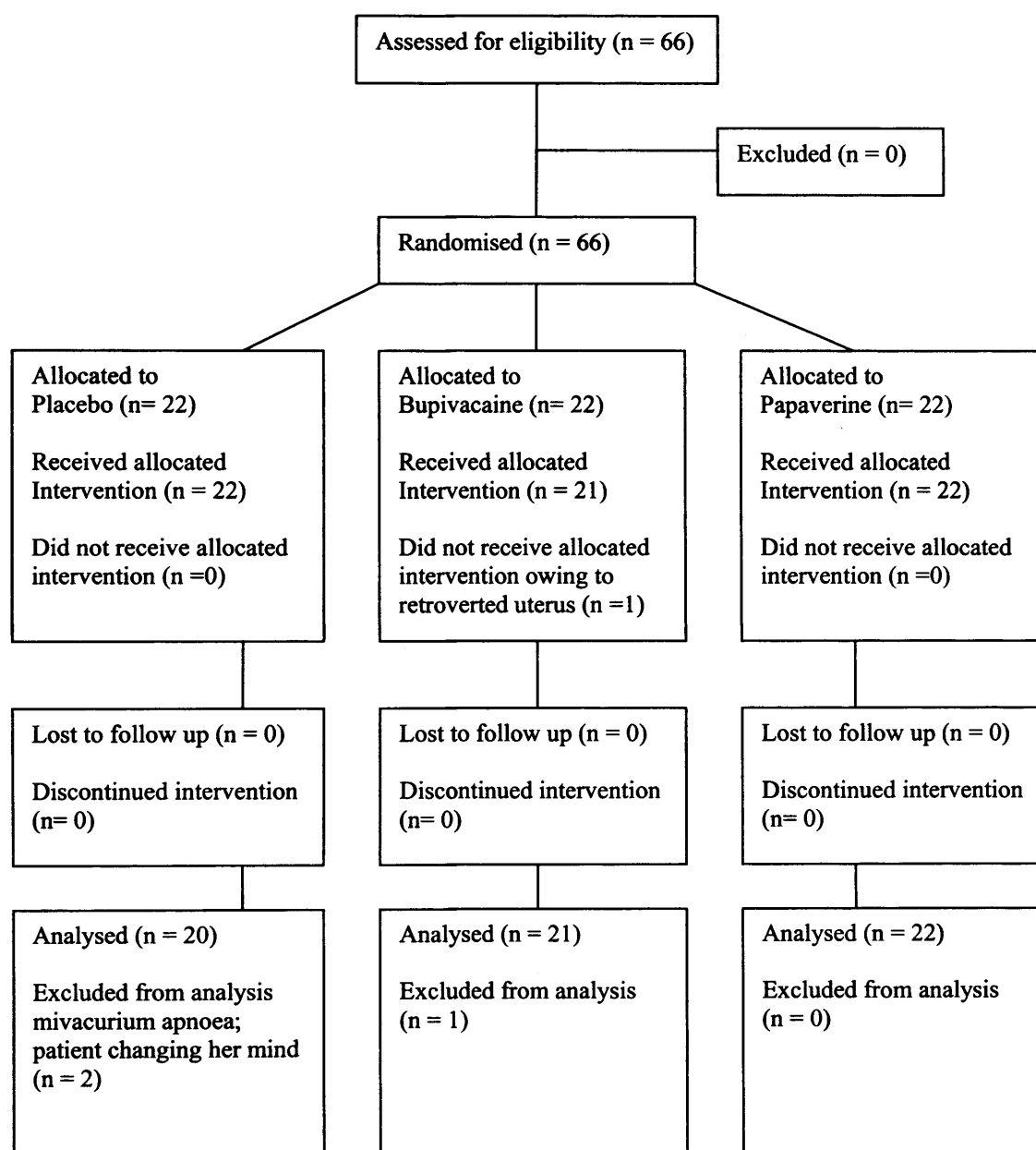
**Table 3.17. Antiemetic consumption, PONV**

<b>Side Effect</b>	<b>Placebo</b>	<b>Bupivacaine</b>	<b>Papaverine</b>	<b>p</b>
PONV	5	2	5	ns
Antiemetic given	3	2	3	ns

Data shown as number of patients and were analysed by the chi-squared test.

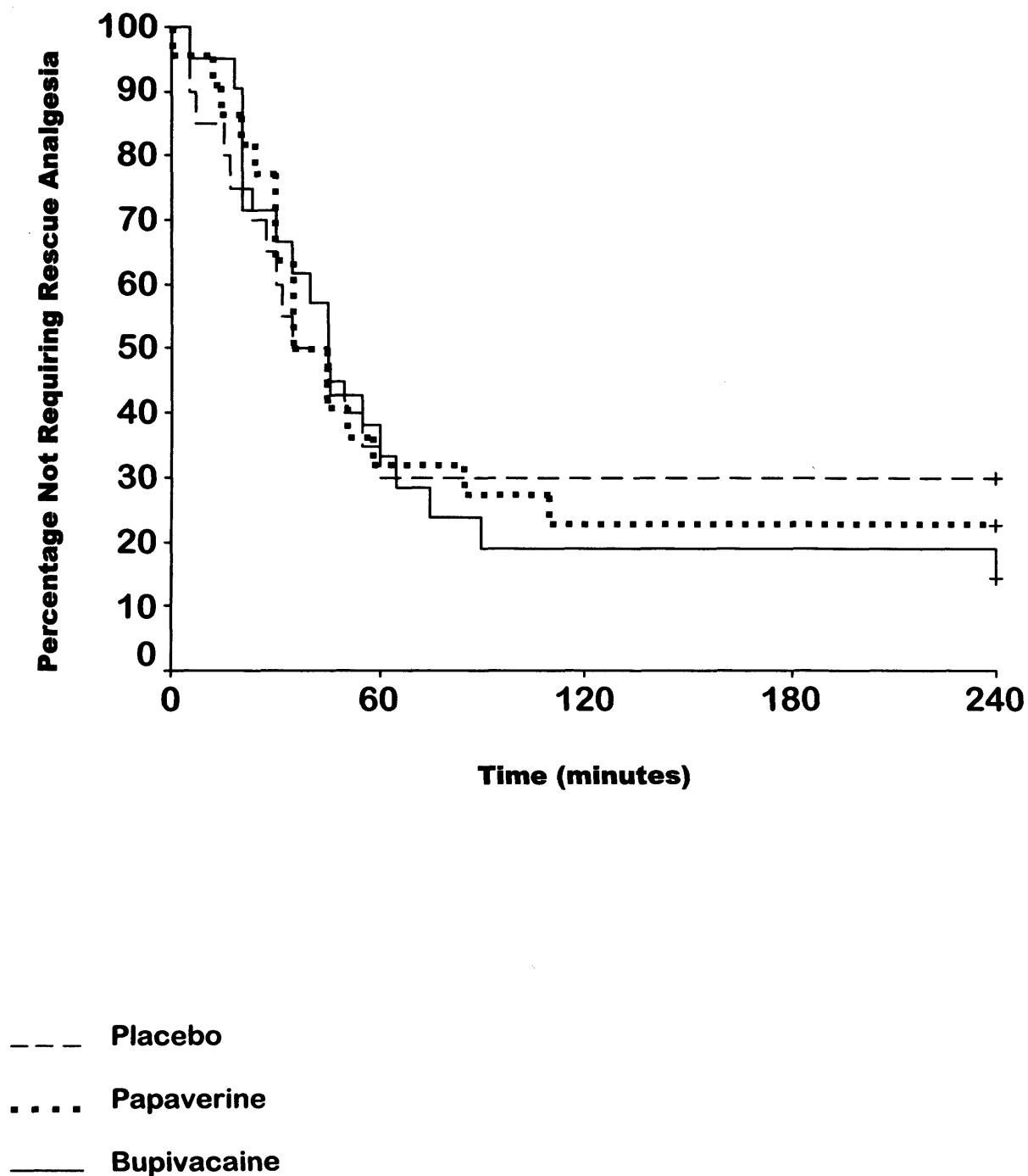
### 3.3.5. Figures

**Fig 3.3. Enrollment, intervention allocation, follow-up and data analysis**



**Fig 3.4. Time To First Analgesia In the Postoperative Period**

(Kaplan Meier Survival Analysis)



## **Chapter 4**

### **Administration of NSAIDs**

#### **4.1. Administration of a non-selective NSAID**

**Does the opioid sparing effect of rectal diclofenac benefit patients following TAH?**

##### **4.1.1. Introduction**

Patients experience much abdominal pain within the first 24 h of their TAH. At our institution, the current standard analgesic for this group of patients is intravenous morphine via a PCA device. The consumption of morphine is high, especially in the initial postoperative period (Stanley 1996, Woodhouse 1998). Morphine may cause adverse effects such as sedation, nausea and vomiting. It is very important to facilitate rehabilitation after surgery and so other methods of analgesia are needed to minimise consumption of morphine.

Diclofenac is a non-selective NSAID that reduces morphine consumption after TAH (Cobby 1999, Scott 1997). The aim of this study was to assess if decreased morphine consumption is associated with a reduction in sedation, nausea and vomiting, in addition to improved analgesia. It is believed that elimination of these adverse effects will go along way to improving the quality of postoperative analgesia and convalescence.

#### **4.1.2. Methods**

After obtaining local institutional Research Ethics Committee approval and informed patient consent, I studied 40 ASA I-II patients, aged 20 to 60 years, scheduled for a TAH. Patients were excluded if the TAH was scheduled for malignancy or if there was a history of chronic pain, continuous usage of analgesic drugs, inability to have diclofenac or inability to use the PCA device.

All patients were given a standardised anaesthetic comprising propofol 2-4 ml kg<sup>-1</sup>, a non-depolarising muscle relaxant, morphine 10 mg iv and prochlorperazine 12.5 mg im. Their lungs were ventilated with nitrous oxide and isoflurane in oxygen, via a tracheal tube. At the end surgery, residual neuromuscular blockade was antagonised with a mixture of neostigmine 2.5 mg and glycopyrrolate 500 µg.

Patients were allocated randomly to receive diclofenac or placebo. Identically-looking suppositories of either diclofenac 75 mg or placebo were prepared specially and randomised (Table 4.1.) by our pharmacy. Each patient was allocated to a numbered container with four of the same suppositories. The first suppository of either diclofenac 75mg or placebo was given after induction of anaesthesia. Subsequently, suppositories of the same content were given on three occasions, at twelve hourly intervals.

In the postoperative period, assessments were made by a member of staff blinded to the treatment, on awakening and then at 8 h, 12 h and 24 h. Sedation, nausea and pain at rest and on movement (deep inspiration) were assessed on a VAS of 0 mm to

100 mm. Patients who were too drowsy to assess themselves were scored as 100 mm for sedation and 0 mm for nausea by the observer. In addition, the number of instances of vomiting and the number of doses of rescue antiemetic were recorded. Morphine consumption was recorded by the PCA device.

We considered that in order to avoid the potential adverse effects of morphine, diclofenac should be able to reduce morphine consumption in the postoperative period by 50%; this reduction was considered clinically important because smaller reductions in morphine consumption have not been associated with improvements in adverse effects (Cobby 1999). From a previous study on NSAIDs, it was estimated that to have an 80% chance of detecting a 50% reduction in 24 h morphine consumption of 38 mg, 16 patients per group would have to be studied (Thompson 2000).

Data were analysed in Excel 2000 and SPSS 9.5. To assess the cumulative adverse effects over the 24 h period, pain scores at rest and on movement, sedation scores, nausea scores, number of vomiting episodes and number of antiemetic administrations were summed from the values taken on awakening, at 8 h, 12 h and 24 h. Data were assessed for normality using Kolmogorov-Smirnov test. Data were analysed using chi-squared test, t-test and Mann-Whitney test, as appropriate.  $P < 0.05$  was considered statistically significant.

#### **4.1.3. Results**

Of 40 patients, 6 did not complete the study. In the diclofenac group, one patient had a midline incision and another patient withdrew herself from the study. In the placebo group, at least one suppository was omitted in 2 patients, one patient had inadequate pain relief and haematemesis occurred in one patient.

Of the remaining patients, there were no significant difference between the two treatment groups in age, weight, ASA status and duration of surgery (Table 4.2.). However, median (interquartile range) 24 h morphine consumption of 31(14-65) mg in the diclofenac group was significantly ( $p=0.02$ ) lower than that of 59(45-85) mg in the placebo group. Mean (95% CI) total pain scores at rest and on movement of 85(51-102) mm and 130(86-152) mm respectively in the diclofenac group were significantly lower than those of 132(105-146) mm and 213(175-231) mm respectively, in the placebo group. In addition, mean (95% CI) total sedation of 90(54-127) mm and median (interquartile range) total nausea of 14(0-53) mm in patients who had diclofenac were significantly lower than the respective scores of 148(100-196) mm and 64(30-109) mm, in patients who had placebo. Despite these benefits, no significant difference in total vomiting episodes or total antiemetic administration was detected between the two groups (Table 4.3.).

#### 4.1.4. Table of results

**Table 4.1. Randomisation of treatment**

Patient no	Code	Treatment
1	1	Diclofenac
2	0	Placebo
3	0	Placebo
4	1	Diclofenac
5	1	Diclofenac
6	0	Placebo
7	1	Diclofenac
8	0	Placebo
9	0	Placebo
10	0	Placebo
11	1	Diclofenac
12	0	Placebo
13	1	Diclofenac
14	0	Placebo
15	1	Diclofenac

**Table 4.1. Randomisation of treatment**

<b>Patient no</b>	<b>Code</b>	<b>Treatment</b>
16	1	Diclofenac
17	0	Placebo
18	1	Diclofenac
19	0	Placebo
20	1	Diclofenac
21	0	Placebo
22	0	Placebo
23	1	Diclofenac
24	0	Placebo
25	1	Diclofenac
26	1	Diclofenac
27	1	Diclofenac
28	0	Placebo
29	0	Placebo
30	1	Diclofenac

**Table 4.1. Randomisation of treatment**

<b>Patient no</b>	<b>Code</b>	<b>Treatment</b>
31	0	Placebo
32	1	Diclofenac
33	1	Diclofenac
34	0	Placebo
35	1	Diclofenac
36	0	Placebo
37	1	Diclofenac
38	0	Placebo
39	1	Diclofenac
40	0	Placebo

**Table 4.2. Baseline characteristics**

	<b>Placebo</b> n=16	<b>Diclofenac</b> n=18	<b>p</b>
Age (yr)	44(40-46)	46(42-48)	ns
Weight (kg)	74(65-78)	71(67-73)	ns
ASA I/II	8/8	12/6	ns
Duration of surgery (min)	65(55-70)	75(65-80)	ns

Data expressed as mean (95% CI) are age, weight and duration of surgery. They were analysed using the unpaired two tailed Student t test.

ASA status was analysed by the chi-squared test.

**Table 4.3. Results**

	<b>Placebo</b> n=16	<b>Diclofenac</b> n=18	<b>p</b>
24h morphine consumption (mg)	59(45-85)	31(14-65)	0.02
Total pain at rest (mm)	132(105-146)	85(51-102)	0.04
Total pain on movement (mm)	213(175-231)	130(86-152)	< 0.01
Total sedation (mm)	148(100-196)	90(54-127)	0.04
Total nausea (mm)	64(30-109)	14(0-53)	< 0.01
Total number of vomiting episodes	0(0-0)	0(0-1)	ns
Total antiemetic administrations	1(0-2)	1(0-1)	ns

Data expressed as mean (95% CI) are total pain at rest, total pain on movement and sedation. They were analysed using the unpaired two tailed Student t test.

Data expressed as median (interquartile range) are 24 h morphine consumption, total nausea, total vomiting episodes and total antiemetic administrations. They were analysed using the Mann Whitney U test.

Total nausea and total sedation were the sum of the scores at 0, 8, 12 and 24 h.

## **4.2. Administration of a COX-2 inhibitor**

**Does the opioid sparing effect of iv parecoxib benefit the patient following TAH?**

### **4.2.1. Introduction**

The background to this study is similar to that described for the previous study on diclofenac.

At our institution, the current management of postoperative pain following TAH involves the use of morphine administered by a PCA device. The dose of morphine is high, particularly in the initial postoperative period (Ng, Swami, Smith 2002; Stanley 1996). Administration of morphine is associated with adverse effects such as delay in return of bowel motility, nausea and vomiting, in addition to sedation (Ng, Parker 2002). Thus other analgesics such as NSAIDs are used to reduce the dose of morphine and hence minimise postoperative morbidity associated with the use of this opioid (Montgomery 1996). Currently available NSAIDs such as diclofenac and ketorolac (Gillis 1997) are non-selective inhibitors of both COX-1 and COX-2 enzymes. Parecoxib is the only currently available intravenous COX-2 selective inhibitor and hence it is suitable for administration in the perioperative period (Cheer 2001). The aim of this study was to investigate if the morphine sparing effect of parecoxib is associated with reductions in postoperative pain intensity, nausea, vomiting, consumption of rescue antiemetics and sedation.

#### **4.2.2. Methods**

After obtaining local research Ethics Committee approval and informed patient consent, I studied 48 ASA I-II patients undergoing TAH via a Pfannenstiel incision. Patients with diagnosed malignancy or with chronic pain were excluded. In addition, we did not selective patients who would be sensitive to drugs used in the study eg history of aspirin induced asthma.

All patients were given a standardised general anaesthetic as described in the previous study on diclofenac. For postoperative analgesia, patients received morphine by PCA delivering morphine 1 mg iv with a lockout time of 5 min. For escape analgesia, patients were allowed a bolus of morphine 5 mg iv.

Patients were allocated randomly to receive either parecoxib 40 mg iv in 2 ml or 2 ml of normal saline on induction of anaesthesia. Both solutions were colourless and were prepared from instructions in an opaque envelope by an anaesthetist who was not involved further in the study. Allocation of treatment was performed randomly by computer, in blocks of 6 (Table 4.4.).

Hourly morphine consumption was recorded from the PCA device. In addition, pain assessments were made on awakening, and then at 1 h, 4 h, 8 h, 12 h and 24 h, by a member of staff blinded to the treatment. Abdominal pain intensity, at rest, on deep inspiration and on sitting up was assessed using the VAS. Patients marked a point on the 100 mm horizontal line representing their pain ranging from “no pain” on the left to “worst ever pain” on the right.

Nausea and sedation were also assessed on visual analogue scales ranging from 0 mm for no nausea and fully awake to 100 mm for worst possible nausea and very drowsy, respectively. Patients who were too drowsy to assess themselves were scored at 100 mm for sedation and 0 mm for nausea. In addition the number of instances of vomiting and number of doses of rescue antiemetic were recorded.

From previous data (Tang 2001), we estimated that to have an 80% chance of detecting a 35% reduction in 24 h morphine consumption at a level of  $P < 0.05$ , a population of 42 patients was required. Data were analysed using Excel 2000 and SPSS 9.5. Data were assessed for normality using the Kolmogorov-Smirnov test. Data were analysed using the chi-squared test, t-test, Mann Whitney test, and analysis of variance for repeated measures.  $P < 0.05$  was considered statistically significant.

#### **4.2.3. Results**

Of 48 patients, 12 did not complete the study because of surgical and analgesic violations. After further examination under general anaesthesia, four patients had a midline incision, 1 patient had an abscess and so TAH was not performed, 1 patient had an abdominoplasty in addition to a TAH and 1 patient had a subtotal abdominal hysterectomy. The PCA failed to work on the ward in 1 patient, the iv cannula tissueed in another patient, and paracetamol and pethidine were given to 2 and 1 patients respectively.

Of the remaining 36 patients, there was no significant difference between the treatment groups in age, weight, ASA status, duration of surgery (Table 4.5.) or intraoperative administration of morphine. However, mean (95% CI) 24 h morphine consumption of 54(42-65) mg in the parecoxib group was significantly ( $P = 0.04$ ) lower than that of 72(58-86) mg in the placebo group (Table 4.6.). In addition pain intensity scores on sitting up were significantly ( $P=0.02$ ) lower in the parecoxib group than in the placebo group. There was no significant difference between the two groups in pain intensity scores at rest and on deep inspiration, total number of vomiting episodes, median number of rescue antiemetic doses, nausea or sedation (Table 4.7.).

#### 4.2.4. Tables of results

**Table 4.4. Randomisation of treatment**

Patient no	Block no	Random no	Treatment
1	1	0.54865	Parecoxib
2	1	0.313402	Placebo
3	1	0.902361	Parecoxib
4	1	0.29575	Placebo
5	1	0.133727	Placebo
6	1	0.498187	Parecoxib
7	2	0.301954	Parecoxib
8	2	0.219661	Placebo
9	2	0.771121	Parecoxib
10	2	0.389073	Parecoxib
11	2	0.505956	Placebo
12	2	0.205128	Placebo
13	3	0.827254	Parecoxib
14	3	0.696804	Placebo
15	3	0.668377	Parecoxib

**Table 4.4. Randomisation of treatment**

<b>Patient no</b>	<b>Block no</b>	<b>Random no</b>	<b>Treatment</b>
16	3	0.321819	Placebo
17	3	0.519816	Placebo
18	3	0.792243	Parecoxib
19	4	0.344853	Placebo
20	4	0.014318	Placebo
21	4	0.225909	Parecoxib
22	4	0.823543	Placebo
23	4	0.86011	Parecoxib
24	4	0.35588	Parecoxib
25	5	0.676284	Placebo
26	5	0.845639	Parecoxib
27	5	0.801816	Parecoxib
28	5	0.235362	Parecoxib
29	5	0.313356	Placebo
30	5	0.995885	Placebo

**Table 4.4. Randomisation of treatment**

Patient no	Block no	Random no	Treatment
31	6	0.368645	Parecoxib
32	6	0.703629	Placebo
33	6	0.410332	Parecoxib
34	6	0.54816	Placebo
35	6	0.692512	Placebo
36	6	0.675817	Parecoxib
37	7	0.944673	Placebo
38	7	0.63924	Parecoxib
39	7	0.304015	Placebo
40	7	0.185045	Parecoxib
41	7	0.082384	Placebo
42	7	0.842931	Parecoxib
43	8	0.406295	Parecoxib
44	8	0.813175	Parecoxib
45	8	0.311672	Placebo
46	8	0.144446	Placebo
47	8	0.438357	Parecoxib
48	8	0.53407	Placebo

**Table 4.5. Baseline characteristics**

	<b>Placebo</b> n=17	<b>Parecoxib</b> n=19
Age (y)	40(37-50)	43(38-47)
Weight (kg)	72(67-77)	69(62-75)
ASA I/II	13/4	14/5
Duration of anaesthesia (min)	73(59-88)	72(59-84)

Baseline characteristics.

Weight and duration of anaesthesia are expressed as mean (95% CI). They were analysed using the unpaired two tailed Student t test.

Age is expressed as median (interquartile range) and was analysed using the Mann Whitney U test.

ASA status was analysed using the chi-squared test.

No significant difference between groups.

**Table 4.6.**

<b>Morphine consumption, episodes of vomiting and rescue antiemetic consumption.</b>			
	<b>Placebo</b>	<b>Parecoxib</b>	<b>p</b>
Intraoperative dose of morphine (mg)	10(10-11)	10.(10-10)	ns
Postoperative dose of morphine (mg)	72(58-86)	54(42-65)	0.04
Total number of vomiting episodes	0(0-0)	0(0-0)	ns
Total number of rescue antiemetic doses	2(1-2.5)	2(1-2)	0.06

Intraoperative morphine dosage and postoperative 24 h morphine consumption are expressed as mean (95% CI). They were analysed by the unpaired two-tailed Student t test.

Total vomiting episodes, total antiemetic administrations postoperatively are expressed as median (interquartile range) and were analysed using the Mann Whitney U test.

Statistical significance when  $P < 0.05$ .

ns, not significant

**Table 4.7. Visual analogue scores (mm)**

	<b>Time (h)</b>	<b>Placebo</b>	<b>Parecoxib</b>	<b>p</b>
<b>Pain intensity at rest</b>	0	66(47-85)	63(43-74)	ns
	1	64(50-73)	60(48-90)	
	4	38(17-71)	38(15-49)	
	8	23(8-45)	34(13-49)	
	12	17(10-35)	17(5-29)	
	24	34(8-51)	26(11-50)	
<b>Pain intensity on inspiration</b>	0	71(66-73)	52(26-84)	ns
	1	66(49-77)	49(45-93)	
	4	37(17-79)	43(18-51)	
	8	32(23-58)	38(14-47)	
	12	22(18-35)	19(7-32)	
	24	25(16-44)	40(16-75)	
<b>Pain intensity on sitting up</b>	0	82(65-90)	87(49-99)	0.02
	1	84(73-99)	64(29-89)	
	4	69(45-85)	44(35-81)	
	8	74(54-85)	49(27-59)	
	12	60(44-71)	49(18-74)	
	24	59(29-78)	49(28-78)	

**Table 4.7. (continued)**

	<b>Time (h)</b>	<b>Placebo</b>	<b>Parecoxib</b>	<b>p</b>
<b>Nausea</b>	0	0(0-38)	0(0-29)	ns
	1	7(0-18)	9(0-42)	
	4	24(1-68)	11(0-31)	
	8	8(4-59)	12(3-22)	
	12	9(6-23)	0(0-16)	
	24	15(1-33)	6(0-21)	
<b>Sedation</b>	0	64(51-82)	78(65-87)	ns
	1	82(43-88)	85(72-92)	
	4	39(30-68)	78(73-90)	
	8	67(51-79)	70(52-81)	
	12	16(10-75)	81(54-96)	
	24	47(36-77)	38(26-69)	

Pain intensity, nausea, and sedation are expressed as median (interquartile range).

Analysis of variance for repeated measures.

No significant difference in any comparison with the exception of pain on sitting.

## Chapter 5

### Discussion

#### **5.1. Local anaesthetics**

We assessed the analgesic effects of local anaesthetics in patients having major abdominal surgery, ie TAH, and in those having minimally invasive surgery, ie laparoscopic cholecystectomy and laparoscopic sterilisation.

##### **5.1.1. The analgesic effects of intraperitoneal and incisional bupivacaine with epinephrine following total abdominal hysterectomy.**

Following TAH, we found that a combination of incisional and intraperitoneal bupivacaine with epinephrine reduced 24 h ( $P<0.01$ ) morphine consumption significantly compared with placebo. On awakening, pain scores on movement ( $P=0.01$ ) were significantly less in the bupivacaine group compared with the placebo group. With the exception of the low median (interquartile range) sedation score of 1(0-2) in the bupivacaine group and 0(0-0) in the placebo group at 24h, there were no significant differences in sedation and nausea scores between the two groups.

The difference in 24 h morphine consumption resulted from a significant reduction in the first 4 h ( $P<0.01$ ) postoperatively. The lack of difference in morphine consumption beyond 4 h may be explained by the metabolism of bupivacaine and hence loss of local anaesthetic effect. As there was no trend to a difference in

morphine consumption between the two groups beyond 4 h, it is unlikely that a type II error has occurred. However, if such a trend occurred, then it would have been necessary to study additional patients, to make up for those who were withdrawn from the study.

No adverse effects were attributable to either local anaesthetic or epinephrine. This observation is consistent with pharmacokinetic studies in which no adverse clinical effects were reported from intraperitoneal bupivacaine (Raetzell 1995)(Lipscomb 1994)(Narchi 1992). In these studies, bupivacaine was administered in doses similar to that of our study and peak plasma concentrations were much lower than the generally accepted toxic value of  $3 \mu\text{g ml}^{-1}$  (Liu 2001).

In patients undergoing TAH, either incisional (Klein 2000)(Leung 2000)(Cobby 1997) or intraperitoneal (Ali 1998) administration of local anaesthetic during surgery has not produced demonstrable reduction in postoperative morphine consumption. In patients having open cholecystectomy, Caesarean section and major abdominal surgery, the evidence for instillation of local anaesthetics into the incision has been equivocal (Moiniche 1998). These negative results contrast with postoperative patient-controlled incisional instillation of local anaesthetic following TAH. In this study in which bupivacaine 0.25% was administered to the wound through a catheter, postoperative opioid consumption as well as incidence of nausea, and ondansetron administration were significantly less in the bupivacaine group compared with the placebo group (Zohar 2001).

It is possible that either introperative incisional or intraperitoneal local anaesthetics given alone may not be adequate to produce measurable postoperative analgesia. Our data suggest that blockade of both visceral and somatic conduction is important if an analgesic sparing effect is to be demonstrated following major surgery such as TAH. Our results do not explain why only incisional administration in the postoperative period by PCA (Zohar 2001) but not incisional administration at the time of TAH (Klein 2000) produces an opioid sparing effect. Patients administering bupivacaine into their wound by PCA used a higher dose over the 24 h study period and it is possible that visceral nociceptive conduction was blocked following systemic absorption. This hypothesis is supported by the systemic action of lidocaine. In a clinical trial of 40 patients undergoing radical retropubic prostatectomy, iv lidocaine was associated with significantly reduced morphine consumption and total pain scores compared with placebo (Groudine 1998). From rat models, it is thought that systemic lidocaine has peripheral and central actions. Peripherally, it suppressed ectopic impulse discharge (Devor 1992) and centrally, it inhibited excitatory responses to iontophoretic glutamate (Biella 1993).

We conclude that a combination of incisional and intraperitoneal bupivacaine with epinephrine may be recommended because it reduces pain on movement on awakening, and provides significant supplemental morphine-sparing analgesia for 4 h after TAH. Unfortunately, we were unable to demonstrate any significant difference in PONV or sedation between the two treatment groups, resulting from the reduction in morphine requirements in the first 4 h.

### **5.1.2. Is intraperitoneal levobupivacaine with epinephrine useful for analgesia following laparoscopic cholecystectomy?**

Following laparoscopic cholecystectomy, we have shown that intraperitoneal instillation of 30 ml of levobupivacaine 2.5 mg ml<sup>-1</sup> with epinephrine 5 µg ml<sup>-1</sup> was associated with significantly reduced ( $p < 0.05$ ) total abdominal pain on inspiration compared with placebo. Total abdominal pain at rest and right shoulder pain were lower but not significantly so in the levobupivacaine group compared with the placebo group. In addition, there was no significant difference between the two groups in total left shoulder pain, incisional pain, sedation, nausea, episodes of vomiting, or rescue morphine and dihydrocodeine consumption. It is possible that we were unable to find a difference in rescue morphine consumption between the two groups because of the low morphine consumption in our study compared with the higher dose in our pilot data.

However, our results are consistent with those of other studies in which intraperitoneal administration of local anaesthetic during laparoscopic cholecystectomy was shown to have a modest analgesic effect. Of 13 clinical trials in a systematic review, it was found that intraperitoneal administration of bupivacaine 50 mg to 200 mg, in volumes of 10 ml to 100 ml, was associated with significant analgesia in 7 studies but not in the other six. In 5 of the studies only, supplemental analgesic consumption was reduced significantly (Moiniche 2000).

In many previous RCTs of laparoscopic cholecystectomy, no distinction has been made between visceral and incisional pain. Intraperitoneal local anaesthetics would be expected to be useful for treatment of the former but not the latter. In the present study, it is likely that intraperitoneal levobupivacaine in the right hypochondrial area had an analgesic effect. It reduced significantly total abdominal pain on inspiration and there was a trend to lower scores for total abdominal pain at rest and total right shoulder pain. As expected, it had no analgesic effect on left shoulder pain or pain from incisional sites.

However, the analgesic effect observed in our study was modest possibly because of the inadequate dose used and rapid dilution of local anaesthetic in the peritoneal cavity. We used a total dose of 125 mg of levobupivacaine of which only 75 mg in 30 ml were instilled into the peritoneal cavity. It is not recommended, however, that the dose of levobupivacaine be increased because of the risk of systemic toxicity.

In conclusion, we found that, compared with placebo, intraperitoneal instillation of levobupivacaine with epinephrine reduced total abdominal pain on inspiration, in the immediate postoperative period after laparoscopic cholecystectomy. Although the analgesic effect was modest, this method of analgesia may be recommended for ambulatory surgery, when used in combination with other morphine-sparing techniques.

### **5.1.3. Transcervical administration of bupivacaine for spasmodic pain after laparoscopic sterilisation: a comparison with papaverine and saline**

We found that neither transcervical bupivacaine nor transcervical papaverine improved analgesia significantly following laparoscopic application of Filshie clips. No significant differences in VAS pain scores, rescue analgesic consumption and time to first analgesia were detected between the three groups.

Our results differ from another study in which a similar dose of bupivacaine (50 ml of 0.25%) was associated with significant reduction in consumption of analgesic drugs postoperatively (Hunter 1996). Thus our inability to demonstrate an analgesic effect with bupivacaine compared with placebo is unlikely to be due to inadequate dose. Furthermore, the lack of additional analgesia with papaverine is surprising at first sight. Papaverine is a well known smooth muscle relaxant that would be expected to be effective.

Clinical studies of the use of local anaesthetic and antispasmodic drugs in the treatment of pain after laparoscopic sterilisation have been associated with variable success. Application of lidocaine 2% gel to Filshie clips has been shown to be ineffective in one trial (Barclay 1994) but beneficial in another (Ezech 1995). Lidocaine 1% given intermittently via a catheter placed intraoperatively into the Pouch of Douglas (Haldane 1998) or lidocaine 1% administered into the subserosal aspect of the cornual end of the Fallopian tubes (Fiddes 1996) has been shown to reduce pain intensity after laparoscopic sterilisation. Bupivacaine 0.5% applied

topically to each Fallopian tube under direct vision has been shown to improve postoperative pain intensity and also to increase the time to first analgesia (Wheatley 1994). In addition, intraoperative application of bupivacaine 0.5% to the mesosalpinx via a long suprapubic needle has produced similar benefits (Alexander 1987, Smith 1991). RCTs have also shown that pain may be reduced with glycopyrrolate 300 µg iv (Guard 1996), but not with buscopan (Wilson 1999, Habib 2001).

Our failure to demonstrate a significant analgesic effect may be attributable to the method of administration. Although transcervical administration allowed drugs to be targeted directly to the site of application of Filshie clips, there may have been substantial loss into the peritoneal cavity via the lateral ends of the fallopian tubes, despite careful, slow administration. Thus, administration of bupivacaine and papaverine as a viscous gel may have been a more useful technique and this warrants further investigation.

## 5.2. NSAIDs

### **Does the opioid sparing effect of rectal diclofenac or iv parecoxib benefit the patient following total abdominal hysterectomy?**

We studied the analgesic effects of diclofenac, a non-selective NSAID, and parecoxib, a COX-2 specific inhibitor, in patients scheduled for TAH. We found that rectal diclofenac 75 mg bd or parecoxib 40 mg iv reduced 24 morphine consumption significantly compared with placebo. This reduction amounted to 52% for diclofenac and 26% for parecoxib. Scores of pain intensity at rest and on movement, sedation and nausea were also reduced significantly in the diclofenac group compared with placebo. In the parecoxib study, pain intensity on sitting up was significantly lower in patients receiving parecoxib compared with placebo. However, in contrast to the diclofenac study, there was no significant difference between the parecoxib and placebo groups in pain intensity scores at rest or on deep inspiration, sedation and nausea. The greater reduction in adverse effects after diclofenac compared with parecoxib may be explained from the larger decrease in morphine consumption with the former compared with the latter. This difference is likely to have occurred because parecoxib was used at half its maximum recommended dose compared with diclofenac that was given at its maximum recommended dose. In addition, this attenuated difference may have occurred because of the reduced power in the parecoxib study as result having 12 exclusions. However, it is unlikely that a Type II error has occurred in the analysis of the remaining 36 patients since we were able to show statistically significant differences in morphine consumption and pain intensity between the two treatment groups.

The morphine sparing effects of diclofenac in our study concur with the findings of other studies of diclofenac (Cobby 1999)(Scott 1997). However, in contrast to our study, the latter were not associated with significant reductions in sedation and nausea (Cobby 1999)(Scott 1997)(Montgomery 1996). This difference may be explained by the method of assessment of sedation and nausea. We used visual analogue scales (Klein 2000)(Ali 1998) that were likely to be more sensitive than the categorical ones of previous studies (Cobby 1999)(Montgomery 1996) (Scott 1997). Thus in comparison to other investigations, our findings are of high importance because we have managed to show that a NSAID is useful not only for analgesia and but also for minimising sedation and nausea in the postoperative period. Improvements of the latter are critical if patients are to recover and rehabilitate quickly after surgery.

The results of our diclofenac study concur well with those of a study on ketorolac, another non-selective NSAID. Ketorolac 30 mg reduced both morphine consumption and also sedation on the first postoperative evening (Parker 1994). In contrast, tenoxicam, another non-selective NSAID, at doses of 20 mg or 40 mg iv, did not reduce significantly PCA fentanyl consumption, pain scores or side effects such as nausea, after TAH (Danou 2000).

The 24 h morphine sparing effect of single dose parecoxib 40 mg iv in our patients after TAH is in agreement with that shown by Tang who used double our dose (Tang 2001). Tang showed that there was a reduction in mean 24 h morphine consumption of 36% in the parecoxib group compared with placebo (Tang 2001). This reduction was greater than that of 26% in our study and is consistent with the lower dose of

parecoxib used in our study. However, in contrast to our study, there was no significant difference in pain scores between the two treatment groups in the study by Tang. It is unclear in this previous study how pain was assessed but it is likely that we were able to detect a difference in pain scores because our assessment of pain on sitting up was more sensitive than assessments made at rest or on deep inspiration.

Meloxicam, a preferential COX-2 inhibitor, has also been studied as a postoperative analgesic adjuvant (Thompson 2000). In a placebo controlled RCT involving patients undergoing TAH, it was shown that rectal meloxicam 15 mg, the maximum recommended daily dose, produced significant reductions in pain scores at rest, on coughing and on sitting. However, in contrast to our studies of diclofenac and parecoxib, meloxicam did not significantly reduce 24 h morphine consumption.

We have shown that both diclofenac and parecoxib are useful analgesic drugs postoperatively. They affect the COX enzymes that are important physiologically for the formation of prostaglandins (PG). COX enzymes catalyse the conversion of arachidonic acid to  $\text{PGH}_2$  via  $\text{PGG}_2$ .  $\text{PGH}_2$  is then converted by a variety of tissue-specific enzymes to other prostaglandins and thromboxanes that have various biological actions. COX-1 is expressed constitutively in normal tissues as part of normal cellular function whereas COX-2 is upregulated during inflammation. Thus, inhibition of COX-2 is desirable because of possible anti-inflammatory and analgesic effects (Cheer 2001). On the other hand, inhibition of COX-1 is theoretically undesirable owing to the reduction in prostaglandins that maintain normal physiological functions eg gastrointestinal integrity. Thus, although traditional non-selective NSAIDs such as diclofenac provide postoperative analgesia, they are

associated with adverse effects that are related, in part, to COX-1 inhibition: these include gastrointestinal ulceration, renal failure and bleeding (Reinhart 2000). In the perioperative period, many patients are at risk of these problems owing to enforced starvation, dehydration and tissue trauma. Whilst adverse effects are uncommon with non-selective COX inhibitors in healthy patients, their use in patients with peptic ulcer disease and renal impairment is contraindicated. A possible alternative in patients at risk of these problems is administration of a selective COX inhibitor eg parecoxib for its improved profile of adverse effects. Previous studies of COX-2 inhibitors, in particular the CLASS (Silverstein 2000) and VIGOR (Bombardier 2000) studies, have been reviewed in Chapter 1.

## Chapter 6

### Conclusion

We have shown that for major procedures such as TAH, non-selective NSAIDS, COX-2 inhibitors and a combination of incisional and intraperitoneal administration of local anaesthetics are associated with useful morphine sparing analgesia. We have also shown that intraperitoneal but not transcervical administration of local anaesthetics is associated with some analgesic effect after laparoscopy.

Intraperitoneal instillation of local anaesthetics is a simple method of analgesia and should be considered in addition to other morphine-sparing analgesics. In high doses the risk of systemic toxicity may be minimised by the use of levobupivacaine rather than racemic bupivacaine, and also by the addition of epinephrine that minimises systemic absorption and hence reduces peak plasma concentrations of local anaesthetic.

Administration of local anaesthetics in biodegradable polymer microcapsules has been investigated recently in human volunteers. In this study, it was shown that duration of analgesia occurred for at least 24 h after intercostal administration of microcapsules of bupivacaine 2.5% 6 ml (Kopacz 2003). Maximum mean (SE) plasma concentration of bupivacaine was  $164.9 \text{ ng ml}^{-1}$  after 15 h. Compared with the latter, it was shown that duration of analgesia was prolonged significantly in volunteers who had microcapsules containing a combination of dexamethasone 0.04% and bupivacaine 2.5%; maximum mean (SE) plasma concentration of bupivacaine was  $101.6(9.7) \text{ ng ml}^{-1}$  after 13 h.

The delivery of local anaesthetic in microcapsules appears to be associated with effective intercostal analgesia. It is envisaged that if long lasting analgesia after TAH, laparoscopic cholecystectomy and laparoscopic sterilisation could be achieved by this type of preparation, then the use of strong opioids such as morphine would be obviated and management of PONV would be made much easier.

Despite the possible theoretical benefits of selective COX-2 inhibitors compared with non-selective NSAIDs, their role in postoperative pain management remains to be determined. They may be useful in patients at risk of gastroduodenal ulceration or after procedures such as tonsillectomy when postoperative haemorrhage is an uncommon but significant problem. However, COX-2 inhibitors appear to impair renal function in a manner similar to that of non-selective NSAIDs and so it is likely that they will not be administered to patients with renal dysfunction. In addition, there is controversy concerning the use of COX-2 inhibitors in patients with coronary heart disease. From recent data, it would appear that the risk of an ischaemic cardiovascular event is increased with rofecoxib but not with other COX-2 inhibitors. In absence of further clarification, it would seem prudent to minimise use of rofecoxib and possibly other COX-2 inhibitors in patients with ischaemic heart disease.

In addition to selective COX-2 inhibitors, non-selective NSAIDs are undergoing further development to minimise their toxicity and enhance their efficacy. There has been chiral manipulation to produce S enantiomers of naproxen, ibuprofen and ketoprofen (Evans 1992)(Burke 2002). In comparison with R enantiomers, S enantiomers have been shown to be associated with COX-2 inhibition and hence

probable analgesia (Carabaza 1996). Further clinical studies are needed to see if these enantiomers are useful for the management of postoperative pain.

On the horizon, nitric oxide-NSAIDs (NO-NSAIDs) are currently under going preclinical, phase I and phase II trials (Fiorucci 2001). NO-NSAIDs are generated by adding a nitrooxybutyl moiety to the parent non-selective NSAID via a short chain ester linkage. Their analgesic, anti-inflammatory and anti-thrombotic properties may be explained in part by non-selective COX inhibition and suppression of prostaglandin synthesis. However, this class of drugs has NO-dependent actions that are independent of COX inhibition. There is NO-dependent anti-thrombotic activity via vasodilatation and inhibition of platelet inhibition. In addition, NO-NSAIDs are anti-inflammatory because they inhibit release of proinflammatory cytokines. This activity occurs as a result of nitrosylation of proteases needed for cellular processing and maturation of IL-1 $\beta$  and IL-18. Furthermore, in animals, NO-NSAIDs may be better than currently available NSAIDs because they do not seem to be toxic to the kidney and stomach. Indeed, it has been shown that healing of gastric ulcers in rats was significantly impaired by a COX-2 inhibitor but not by NO-aspirin (Ukawa 1998). It will not be long before NO-NSAIDs become available and we can look forward to see what role they may have in the management of postoperative pain.

With the shift in surgical practice from open to minimally invasive procedures, there is a greater assumption that patients will recover and return to work more quickly. The four "As": alertness, analgesia, ambulation and alimentation must be achieved as quickly as possible (Rawal 2001). Laparoscopic sterilisation and even laparoscopic cholecystectomy are currently considered to be relatively minor operations. Indeed,

they have been classified as basket procedures (analagous to shopping with a supermarket basket) in the UK government's publication on day surgery (Department of Health 2002), and thus the expectation is that patients will be ambulatory soon after surgery. But one factor limiting patient recovery is postoperative pain. Other methods of pain relief such as epidural analgesia [Fujii 1998] and insertion of a suprahepatic suction drain [Jorgensen 1995] have been shown to be useful following laparoscopic cholecystectomy; but these methods are invasive and unsuitable for the practice of ambulatory anaesthesia.

In the postoperative period, pain, sedation, PONV and return of bowel motility are important factors that affect recovery. Reduction in morphine consumption with NSAIDs and local anaesthetics may improve convalescence after surgery. This multimodal approach provides balanced analgesia because inflammation in the periphery, afferent neuronal transmission and central pain processes may be minimised after tissue trauma (Power 1999). However, postoperative recovery is multi-faceted and so a solitary intervention such as provision of pain relief (Rowbotham 2001) is unlikely to alter patient outcome. A multi-modal integrated programme of rehabilitation in the pathway of patient care is needed (Kehlet 2001) and advances in surgery will need to be met by progress in improving anaesthetic morbidity.

Over all, it can be seen from the data presented in this thesis that local anaesthetics and NSAIDs were associated with useful decreases in opioid consumption. However, this effect was small and so their administration in combination, ie triple therapy, would appear to be the most optimal method for pain control after surgery.

## **Chapter 7**

### **Publication of work contained in this thesis**

#### **7.1. Abstracts**

Four abstracts were presented to the Anaesthetic Research Society. After peer review by members of the Society, they were accepted for publication.

Nottingham 23 November 2001.

Ng A, Swami A, Smith G, Davidson AC, Emembolu J. The analgesic effects of intraperitoneal and incisional bupivacaine with epinephrine following total abdominal hysterectomy. *Br J Anaesth* 2002;88:326-7P.

Glasgow, 3 April 2003.

Ng A, Swami A, Smith G, Robertson G, Lloyd D. Intraperitoneal levobupivacaine with epinephrine after laparoscopic cholecystectomy. *Br J Anaesth* 2003;90:820P.

Leeds, 6 July 2001.

Ng A, Habib A, Swami A, Smith G, Davidson AC. Effect of transcervical papaverine and bupivacaine on postoperative analgesia following laparoscopic application of Filshie clips. Br J Anaesth 2001; 663-4P.

London, 13 December 2002.

Ng A, Smith G, Ratcliffe J, Davidson AC. The analgesic effects of parecoxib following total abdominal hysterectomy. Br J Anaesth 2003;422-3P.

## 7.1.1.

Proceedings of the Anaesthetic Research Society

### Intraperitoneal and incisional bupivacaine with epinephrine for analgesia following total abdominal hysterectomy

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Incisional<sup>1</sup> or intraperitoneal<sup>2</sup> local anaesthetic instillation during surgery has not been shown to produce opioid sparing effects compared with placebo. The aim of this prospective double blind randomized placebo controlled trial was to investigate if a combination of intraperitoneal and incisional bupivacaine with epinephrine would reduce morphine consumption following total abdominal hysterectomy (TAH).

We studied 46 ASA I-II patients listed for TAH via a Pfannenstiel incision. Exclusion criteria were malignancy, drug allergy and a chronic pain syndrome. All patients received a standardized anaesthetic of propofol 2–4 mg kg<sup>-1</sup> i.v., a non-depolarizing muscle relaxant, morphine 10 mg i.v., ondansetron 4 mg i.v. and rectal paracetamol 1g. Their lungs were ventilated with nitrous oxide and isoflurane in oxygen via a cuffed tracheal tube. At the end of the procedure, residual neuromuscular blockade was reversed with neostigmine 2.5 mg and glycopyrrolate 500 µg. Postoperatively, patients received i.v. morphine via a patient controlled analgesia (PCA) device and rectal paracetamol 1g 6-hourly. Patients were allocated by computer randomization to receive 50 ml of bupivacaine 0.25% with epinephrine 5 µg ml<sup>-1</sup> or 50 ml of normal saline. Following instructions from sealed opaque envelopes, 30 ml and 20 ml of the treatment solution were administered into the peritoneum and incision respectively before wound closure. Postoperatively, morphine consumption was recorded hourly and assessments of pain at rest and on movement were made by a member of staff blinded to the treatment, on awakening and then at 8, 12 and 24 h.

Seventeen and 16 patients in the placebo and bupivacaine groups, respectively, completed the study. There were no significant differences between the bupivacaine and placebo groups in age, height, weight or duration of surgery. Pain on movement were significantly higher in the placebo group than in the bupivacaine group on awakening. Morphine consumption (interquartile range) over 24 h was 62 (53–85) mg in the placebo group compared with 44 (33–56) mg in the bupivacaine group ( $P < 0.01$ ). This significant difference was attributable to the significantly higher morphine consumption in the placebo group in the first 4 h postoperatively.

**Keywords:** analgesia; anaesthetics local

## Proceedings of the Anaesthetic Research Society

**References**

- 1 Klein JR, Heaton JP, Thompson JP, Cotton BR, Davidson AC, Smith G. *Br J Anaesth* 2000; **84**: 248-9
- 2 Ali PB, Cotton BR, Williamson KM, Smith G. *Br J Anaesth* 1998; **80**: 245-7

## 7.1.2.

Proceedings of the Anaesthetic Research Society

### Intraperitoneal levobupivacaine with epinephrine after laparoscopic cholecystectomy

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Despite being minimally invasive, laparoscopic cholecystectomy (LC) may cause patients to experience severe pain, requiring administration of morphine. In other surgical procedures, the dose of morphine may be reduced by use of local anaesthetics<sup>1,2</sup> and the purpose of the present investigation was to see if i.p. instillation of levobupivacaine with epinephrine reduces morphine consumption and ameliorates visceral and shoulder pain, after LC.

Forty-eight ASA I/II patients listed for LC received a standardized general anaesthetic, including fentanyl  $2\mu\text{g kg}^{-1}$  i.v., diclofenac 100 mg p.r. and paracetamol 1 g p.r., at induction. At the end of surgery, all patients received 20 ml of levobupivacaine  $2.5\text{ mg ml}^{-1}$  with epinephrine  $5\mu\text{g ml}^{-1}$  to incisional sites. Patients were allocated randomly to receive either 30 ml of levobupivacaine  $2.5\text{ mg ml}^{-1}$  with epinephrine  $5\mu\text{g ml}^{-1}$  or 30 ml of normal saline with epinephrine  $5\mu\text{g ml}^{-1}$ , intraperitoneally to the gall bladder bed and above the liver just before wound closure. Postoperatively, patients were assessed on awakening and then at 1, 2, 3, and 4 h; abdominal, incisional and shoulder pain was assessed on a visual analogue scale (VAS) of 0–100 mm. For rescue analgesia in the recovery room, morphine i.v. was given to keep pain VAS less than 35 mm.

Five patients were excluded for protocol violations. Of 43 patients studied, there were no significant differences between the two treatment groups in their baseline characteristics. Median (interquartile range) total abdominal pain on inspiration in the levobupivacaine group (71 (21–129) mm) was significantly ( $P<0.05$ ) lower than that in the placebo group (123 (71–179) mm). However, median (interquartile range) total abdominal pain at rest (72 (35–128) mm) in the levobupivacaine group did not differ significantly ( $P=0.08$ ) from that in the placebo group (101 (76–134) mm). In addition, median (interquartile range) total right shoulder pain of 0 (0–20) mm in the levobupivacaine group did not differ significantly ( $P=0.07$ ) from that of 16 (0–49) mm in the placebo group. Of other pain scores, there were no significant differences between the two groups in total left shoulder pain, total incisional pain at rest or total incisional pain on inspiration. Median (interquartile range) total rescue morphine consumption (0 (0–7) mg) in the levobupivacaine group did not differ significantly from that in the placebo group (2 (0–10) mg). The doses of dihydrocodeine and cyclizine administered in addition to total sedation and total nausea scores, and number of episodes of vomiting did not differ significantly between the two groups.

**Keywords:** anaesthetics local, levobupivacaine; surgery, laparoscopy

### References

- 1 Ng A, Smith G. *Br J Anaesth* 2002; 89: 535–7
- 2 Ng A, Swami A, Smith G, Davidson AC, Emambolu J. *Anesth Analg* 2002; 95: 158–62

## 7.1.3.

Proceedings of the Anaesthetic Research Society

### Effect of transcervical papaverine and bupivacaine on postoperative analgesia after laparoscopic application of filshie clips

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In comparison with diagnostic laparoscopy, Filshie clips applied during laparoscopic sterilization can cause additional abdominal pain induced by ischaemia or spasm. Papaverine is a smooth neuromuscular blocking agent that may improve this pain if administered directly to the fallopian tubes. Previous trials evaluating administration of transcervical bupivacaine<sup>1</sup> and lignocaine<sup>2</sup> to Filshie clips have shown positive results. The aim of the study was to evaluate if transcervical papaverine would reduce this pain and to compare this effect with those of bupivacaine and placebo.

Sixty-six ASA I-II females, undergoing laparoscopic sterilization, were recruited and allocated randomly to either papaverine 30 mg or 0.375% bupivacaine 30 ml or 30 ml of saline. Patients were given a standard anaesthetic comprising propofol 2-4 mg kg<sup>-1</sup>, fentanyl 1 mg kg<sup>-1</sup> and a neuromuscular blocking agent. Patients' lungs were ventilated to normocapnia with nitrous oxide and isoflurane in oxygen via a standard laryngeal mask airway.† Suppositories of diclofenac 100 mg and i.v. ondansetron 4 mg were given. Before application of a Filshie clip to the medial third of each Fallopian tube, the appropriate solution was injected through a Spackman's cannula placed into the cervix of the uterus. Residual neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrrolate 500 mg at the end of surgery.

Postoperatively, rescue analgesia comprised two tablets of cocodamol 30/500 and i.m. morphine 10 mg. Patients were assessed as soon as they were awake (time 0), at 30 min and then at 1, 2, 3, and 4 h by an observer blinded to the treatment. Exclusion criteria were allergies to bupivacaine and papaverine, chronic pain syndrome, pelvic inflammatory disease and adhesions, regular analgesic ingestion and operative difficulties.

Of 66 patients recruited, three did not complete the study. There were no significant differences between the three groups in age and median body mass index. Analgesic consumption did not differ significantly between the groups in terms of: number of patients having analgesia within the first postoperative hour; number of patients having cocodamol only, morphine only or the combination of cocodamol and morphine. There were no significant differences between median visual analogue pain scores, sedation scores, incidence of postoperative nausea and vomiting, and requirement for rescue antiemetics. In conclusion, transcervical papaverine did not provide additional analgesia for laparoscopic sterilization.

**Keywords:** surgery, laparoscopic sterilization; analgesia, postoperative

#### References

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- 2 Esch UO, Shouder VS, Martin JL, et al. *Lancet* 1995; 346: 82-5

## 7.1.4.

Proceedings of the Anaesthetic Research Society and Intensive Care Society

### The analgesic effects of parecoxib after total abdominal hysterectomy

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Patients experience considerable pain after total abdominal hysterectomy (TAH), requiring administration of morphine during the first 24–48 h after surgery. Morphine is associated with adverse effects such as sedation, nausea and vomiting. The aim of this study was to see if parecoxib, an i.v.-administered cyclo-oxygenase-2 inhibitor, reduces morphine consumption and patient morbidity after TAH.

After obtaining local research ethics committee approval and informed patient consent, we studied 48 ASA I–II patients listed for TAH via a Pfannenstiel incision. Patients with malignancy and chronic pain were excluded. All patients were given a standardized anaesthetic including morphine 10 mg.

For postoperative analgesia, patients received morphine by patient-controlled analgesia (PCA), delivering 1 mg i.v. with a lockout time of 5 min. For escape analgesia, patients were allowed boluses of morphine 5 mg. Patients were allocated randomly to either parecoxib 40 mg i.v. in 2 ml or normal saline 2 ml i.v., at induction of anaesthesia. Both solutions were colourless and were prepared independently of the assessor and patient, from instructions in an opaque envelope.

Assessments were made on awakening and then at 1, 4, 8, 12 and 24 h, by a member of staff blinded to the treatment. A visual analogue scale of 0–100 mm was used to assess: intensity of abdominal pain at rest, on deep inspiration and on sitting up; nausea and sedation. The number of episodes of vomiting and doses of antiemetic were recorded.

From previous data,<sup>1</sup> we estimated that, to have an 80% chance of detecting a 35% reduction in 24 h morphine consumption, we would need to study 21 patients per group.

Of 48 patients, seven were excluded for surgical reasons: midline incision, TAH not performed because of an abscess, abdominoplasty and subtotal hysterectomy occurred in four, one, one and one patients, respectively. There were an additional five exclusions for analgesic violations: PCA pump failure, i.v. cannula failure, acetaminophen and meperidine administration in one, one, two and one patients respectively.

Of the 36 patients studied, there was no significant difference between the treatment groups in patient age, weight, ASA status, duration of surgery and intraoperative dose of morphine. However, mean (SD) 24 h morphine consumption of 53.7 (23.6) mg in the parecoxib group was significantly less ( $P < 0.04$ ) than that of 71.8 (28) mg in the placebo group. In addition, pain intensity on sitting up was significantly less ( $P < 0.02$ ) in the parecoxib group than in the placebo group. However, there was no significant difference between the treatment groups in pain intensity at rest, pain intensity on deep inspiration, sedation, nausea, vomiting episodes and antiemetic consumption.

**Acknowledgement:** We are grateful to Pharmacia for providing a research grant for the study.

Proceedings of the Anaesthetic Research Society and Intensive Care Society

**Keywords:** analgesics non-opioid, parecoxib; pain, postoperative; surgery, gynaecological

#### **Reference**

1 Tang J, Chen X, White PF, et al. *Anesth Analg* 2001; 92: S270

## 7.2. Review Article

Aspects of gastrointestinal outcome associated with pain management in the postoperative period have been review in this article.

*J Anesth* (2002) 16:51–64

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**Anesthesia**  
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### Review article

## Anesthesia and the gastrointestinal tract

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**Key words** Gastrointestinal tract · PONV

### Introduction

In this article, we have briefly reviewed areas relating to the gastrointestinal (GI) tract of interest to the anesthesiologist; they include gastroesophageal reflux and aspiration of gastric contents, postoperative nausea and vomiting (PONV), gastrointestinal ileus, and intestinal anastomotic leakages. These areas represent major causes of morbidity and delay in recovery from anesthesia and surgery. In addition, we have briefly described the use of the GI tract for the purpose of drug administration in the perioperative period.

The subjects of regurgitation and aspiration have recently been reviewed by us in some detail [1]; so these areas are summarized only briefly.

### Gastroesophageal reflux and aspiration of gastric contents

#### *Incidence of aspiration and mortality attributable to aspiration*

The incidence of aspiration has remained relatively low over the past three decades. Data from several studies have shown that the incidence varies between 0.7 and 10.2 per 10000 general anesthetics [2–8]. Over this same period, mortality attributable to aspiration during general anesthesia varied between 3.8% [9], 4.5% [3], and 4.6% [2].

In obstetric practice, however, mortality attributable to aspiration has declined over time. The triennial re-

ports of the Confidential Enquiry into Maternal Deaths in the United Kingdom have demonstrated that mortality attributable to aspiration has decreased from 52% to 65% 50 years ago, to 0% to 12% in the last 10 years [10]. Over the same period, there has been an increase in the total number of anesthetics administered, as a result of increasing instrumental rates and deliveries by cesarean section [10]. Therefore, the reduction in the proportion of anesthetic deaths is likely to have been related not only to general improvements in anesthetic training and skills over time, but, more importantly, to the progressive move away from general anesthesia to epidural and spinal anesthesia.

#### *Anesthetic management of gastroesophageal reflux and aspiration of gastric contents*

Anesthetic management of gastroesophageal reflux and aspiration of gastric contents requires the consideration of factors that predispose to aspiration pneumonia and also methods to minimize regurgitation and aspiration (Table 1).

#### *Factors that predispose to aspiration pneumonia*

Gastric contents. Gastric contents that are considered to increase the risk of aspiration pneumonia are a pH less than 2.5 and gastric volume of 0.4 ml·kg<sup>-1</sup> and a composition comprising milk. While there is controversy over the minimum critical gastric volume [11–13] above which the risk of aspiration pneumonia is increased, there is concordance from animal studies that a very low pH (less than 1) [14], and breast milk or a dairy formula [15], predispose to an increased severity of aspiration pneumonia compared with less acidic contents or a soya-based milk [16].

Lower esophageal sphincter (LES) tone. Reduction in tone of the lower esophageal sphincter is an important physiological mechanism for reflux of gastric contents.

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**Table 1.** Management of gastroesophageal reflux and aspiration of gastric contents [1]

Factors predisposing to aspiration pneumonitis	Methods to minimize regurgitation and aspiration
Gastric contents pH < 2.5 Volume >0.4 ml·kg <sup>-1</sup> Human breast milk Dairy milk	Control of gastric contents Preoperative starvation Nasogastric tube Prokinetics Reducing gastric acidity: H <sub>2</sub> antagonists, PPIs
LES and UES Reduced sphincter tone in the lower and upper esophagus during anesthesia	Nasogastric tube with an occluding balloon Application of cricoid pressure Correct timing, magnitude and direction
Protective airway reflexes impaired in the perioperative period: Apnea with laryngospasm Coughing Expiration Spasmodic panting	Careful airway management. Devices to be considered are: Tracheal tube Laryngeal mask airway (LMA) Intubating laryngeal mask airway (ILMA) Esophageal-tracheal combitube (ETC)

PPIs, Proton pump inhibitors; LES, lower esophageal sphincter; UES, upper esophageal sphincter

The factor which inhibits regurgitation is the barrier pressure, i.e., the difference between gastric pressure and LES pressure. During anesthesia, it has been shown that LES pressure and also barrier are decreased by induction agents (thiopental), inhalation agents (halothane and enflurane), opioids, and anticholinergic drugs (glycopyrrolate, atropine) [1].

Upper esophageal sphincter (UES) tone. UES tone is also reduced by induction agents (thiopental) [17], sedative agents [17], and muscle relaxants (succinylcholine [18], atracurium, pancuronium, and vecuronium [19–22]).

However, the risk of aspiration depends not only on UES tone but also on coordination between the pharyngeal muscles and the UES during swallowing. It has been possible to study the deleterious effect of partial neuromuscular blockade on aspiration using video manometry. These studies have been conducted in healthy volunteers, and the extent of neuromuscular blockade adjusted according to the train-of-four (TOF) pattern of adductor pollicis during supramaximal stimulation of the ulnar nerve. Significant delay in relaxation of the UES following contraction of the inferior constrictor muscle begins to occur at a TOF of 0.7 with atracurium [21] and 0.60 with vecuronium [20]. In 28%, 17%, 20%, and 13% of volunteers receiving atracurium, pharyngeal muscle dysfunction occurred at a TOF of 0.60, 0.70, 0.80 and ≥0.90, respectively. Of these swallows with pharyngeal dysfunction, 80% were misdirected, with contrast medium reaching the level of the vocal cords [21]. Although pharyngeal muscle dysfunction was demonstrated in patients given atracurium but not vecuronium, misdirected swallows still occurred in 6 of 14 volunteers at various levels of blockade with vecuronium [20]. These studies suggest that, even with clinically adequate neuromuscular transmission, con-

scious patients in the recovery room may still be at risk of aspiration.

Protective airway reflexes. Airway reflexes are impaired by premedication with diazepam [23], by advancing age [24], and by incremental doses of fentanyl [25], in addition to progressively increasing depth of anesthesia. Loss of these reflexes during anesthesia increases the risk of aspiration pneumonitis.

#### *Methods to minimize regurgitation and aspiration*

Methods to minimize regurgitation and aspiration involve control of gastric contents, application of cricoid pressure, and control of the airway.

Control of gastric contents and application of cricoid pressure. Preoperative starvation is a universal method for controlling gastric contents. Studies on gastric emptying demonstrate that clear fluids, breast milk, non-human milk, and solids are emptied at correspondingly slower rates. From these studies involving paracetamol absorption [26–32], electrical impedance tomography [33–35], radiolabelled diet [32,34,36–39] ultrasonography [40–43], aspiration of gastric contents under direct vision with a gastroscope, polyethylene glycol dilution and blind aspiration of gastric contents, it is generally held that the preoperative starvation time should be 2 h for clear fluids, 4 h for breast milk, and 6 h for nonhuman milk and solids [44].

Gastric emptying has been shown to be inhibited by atropine [45] and opioids [46], but facilitated by erythromycin [47], cisapride [48], and metoclopramide [49]. The presence of a nasogastric tube may impair UES and LES tone [50], leading to gastroesophageal reflux [51]. However, there is evidence from two cadaver studies that the efficacy of cricoid pressure is not

diminished by the presence of a nasogastric tube [52–53].

Evidence from clinical trials clearly shows that  $H_2$  antagonists and proton pump inhibitors (PPIs) are two drug groups that may significantly lower gastric acidity [54–56] and, hence, reduce the risk of aspiration pneumonitis. However, there is no available evidence to support their routine use, probably because of the low incidence of aspiration and multiplicity of factors that are linked to this complication.

To minimize the passage of gastric contents through the esophagus, use of a nasogastric tube with an inflatable balloon to occlude the gastric cardia has been effective in a study involving pigs [57]. Application of cricoid pressure, however, is more usual in anesthetic practice, despite the lack of good evidence to demonstrate that it has reduced the incidence of aspiration or mortality. Recent studies have criticized cricoid pressure because of its effect in lowering LES tone [58], possible cricoid occlusion and vocal cord closure at a pressure of 44 N [59], occurrence of retching if applied too early [60], incorrect direction of application causing impaired laryngoscopy [61], variability in perceived force of application [62], and unsustainable force of application over time [63].

Control of the airway. During general anesthesia, an unobstructed airway is of paramount importance; this issue was highlighted by the Australian Incident Monitoring Study [9], in which the difficult airway was considered to predispose to regurgitation, vomiting, and aspiration.

Although tracheal intubation is considered to be the standard method for airway protection during general anesthesia, recent studies have challenged this view. The main issues are: firstly, whether tracheal intubation is effective; and secondly, whether aspiration is a problem if tracheal intubation is avoided. Clinical trials in the intensive care setting [64,65] have clearly demonstrated that high-volume, low-pressure cuffs do not prevent passage of methylene blue between the longitudinal folds. In addition, a case series of patients anesthetized without tracheal intubation in the peripartum period did not show an increased incidence of aspiration [7]. There was one case of mild aspiration among 1870 patients anesthetized for obstetric procedures, except for cesarean sections.

The standard laryngeal mask airway (LMA) has been evaluated extensively in clinical trials. It appears to reduce barrier pressure [66] and, while promoting gastroesophageal reflux of acid to the lower esophageal level, seems to spare the upper esophageal level [67–69]. The ProSeal LMA (PLMA) is a recent modification of the standard LMA [70]. It has an esophageal vent that allows the passage of a nasogastric tube. Although this

device allows the stomach to be emptied, it remains to be seen whether it will play an important role in minimizing the risk of aspiration pneumonitis.

The esophageal-tracheal combitube (ETC) is a double-lumen tube with a high-volume, low-pressure tracheoesophageal distal cuff and a proximal pharyngeal balloon. The ETC may protect against the risk of aspiration and has been given a role in the American Society of Anesthesiologists (ASA) practice guidelines for the management of the difficult airway [71]. Complications of its use, such as esophageal lacerations, subcutaneous emphysema [72], sore throat, hematoma, and dysphagia, appear to have been related to blind insertions rather than insertions under direct vision [73,74].

### Postoperative nausea and vomiting (PONV)

#### *Clinical trials*

Evidence on the outcome of different treatments for PONV has been collated in quantitative systematic reviews (meta-analysis) of many double-blind randomized controlled trials (RCTs). Although these systematic reviews represent Level One Evidence, some assessment of the treatment effects of the individual trials must be made before a decision is made on whether the pooled results are valid. Overall, the applications of quantitative systematic reviews, as well as their limitations, have been discussed extensively in a recent article by Choi and Jadad [75].

Trials that have had event rates of 20% to 60% for early PONV (0 to 6 h) and 40% to 80% for late PONV (0 to 48 h) have been included in some systematic reviews, excluding studies with extreme values that were not deemed to reflect the overall clinical situation. Treatment effect in many of these reviews has been quantified in terms of relative benefit, relative risk, or odds ratio and also as absolute risk reduction. The relative benefit, relative risk, or odds ratio allows a relative comparison of the outcome of one treatment over another, but does not take into account the magnitude of the problem. However, the absolute risk reduction does take into account the importance of the treatment effect, providing the clinician with more information from which to decide whether the treatment is worth administering. The reciprocal of the absolute risk reduction gives the term “number needed to treat” (NNT). The NNT is the number of patients who have to be treated to obtain one additional favorable outcome [76]. More efficacious treatments have a low NNT, while less useful treatments have a high NNT. All treatments have adverse effects, and in a similar way to the above consideration of benefits, “number needed to harm” (NNH) can be obtained from the reciprocal of absolute risk increase.

### Factors that influence the occurrence of PONV

PONV is more common in females and in patients with a previous history of PONV or motion sickness. It appears to be associated with strabismus surgery, adenotonsillectomy, orchidopexy, and prolonged surgery. Other factors predisposing to its occurrence are the use of etomidate, opioids, and pancuronium, and the use of atropine and neostigmine [77]. Propofol, on the other hand, has the opposite effect, and in a systematic review of 84 RCTs involving 6069 patients, its effect on early and late PONV was assessed [78]. When used for maintenance instead of inhalation agents, propofol had an NNT (95% confidence interval [CI]) of 4.9 (3.7 to 7.1), and 7.1 (3.4 to  $\infty$ ) for early and late PONV, respectively, suggesting that any antiemetic advantage is short lived. Propofol used solely for induction did not confer an advantage over other intravenous agents. In a reassessment [79] of a systematic review of RCTs in which use of nitrous oxide was assessed [80], it was shown that omission of nitrous oxide had beneficial effects on early (NNT 4.8 (3.6 to 7.3)) and late vomiting (NNT 5.6 (3.9 to 10)), but not early (NNT 9.1 (4.1 to  $\infty$ )) or late nausea (NNT  $\infty$  (80)).

### Methods to prevent and treat PONV

A management plan for the prevention of PONV has been summarized in Table 2. Techniques to minimize PONV may be classified into two categories, pharmacological agents and nonpharmacological methods. Studies on readily available pharmacological agents

have compared the use of single agents versus placebo; combination of agents versus single agents; and administration of an antiemetic with an opioid via a patient-controlled analgesic device. In addition, data have been available concerning the possible antiemetic effect of 80% inspired oxygen compared with 30% [81]. In this RCT, oxygen was given intraoperatively and for the first 2h postoperative in patients undergoing colorectal surgery, and it has been found that the higher oxygen concentration had an antiemetic effect.

### Neurokinin (NK)-1 receptor antagonists

NK-1 antagonists are thought to act by blocking the effect of substance P on NK-1 receptors [82]. For the prevention of PONV, evidence from a double-blind RCT of females listed for abdominal hysterectomy demonstrated that 100mg or 200mg of oral CP122721, administered 60 to 90min preoperatively, was more effective than placebo for prevention of PONV within 8h and 72h into the postoperative period [83]. Within the first 8h, the higher dose of this NK-1 antagonist was more effective than the lower dose (the incidences of PONV being 10% and 33%, respectively). This benefit was not demonstrable within 72h. It is possible that further clinical studies may reveal a role for NK-1 antagonists in patients at high risk of PONV.

### 5HT<sub>3</sub> antagonists

Although several 5HT<sub>3</sub> antagonists have been evaluated, ondansetron has been studied most extensively. The efficacy of ondansetron has been assessed for both

**Table 2.** Management of PONV

Plan	Example
Identify the patient at risk	Female sex Nonsmoker Positive history of PONV Positive history of motion sickness Duration of anesthesia >60min
Use an antiemetic anesthetic technique	Use propofol Minimize use of emetogenic agents e.g., opioids, etomidate
Consider specific antiemetic treatments	Individual pharmacological agents NK1 antagonists 5HT <sub>3</sub> antagonists Dexamethasone Droperidol Cyclizine Combination agents 5HT <sub>3</sub> antagonists with cyclizine 5HT <sub>3</sub> antagonist with dexamethasone 5HT <sub>3</sub> antagonist with NK1 antagonist Physical therapy Acupuncture

PONV, Postoperative nausea and vomiting; NK1, Neurokinin

the prophylaxis and treatment of PONV. In a meta-analysis of 53 placebo-controlled RCTs involving 7177 patients, 24 different ondansetron regimens were evaluated [84] for the prevention of PONV. Although a broad range of NNTs were obtained, ondansetron showed treatment benefit (NNT 5 to 6) at 8 mg i.v. and 16 mg orally, for prevention of early and late PONV. In addition, there was a significant increased risk of elevated liver enzymes (NNH of 31) and headache (NNH of 36).

The issue of whether ondansetron is effective in preventing PONV in high-risk patients has been addressed. In a meta-analysis of RCTs, ondansetron 4 mg and 8 mg i.v. showed increased effectiveness for prevention of PONV in patients with motion sickness compared with patients without this history [85]. The pooled odds ratios (95% CI) were 2.07 (1.69–2.52) and 2.19 (1.5–3.19) for the two respective doses. In another meta-analysis comparing patients with and without a previous history of PONV, there was no significant difference in the effectiveness of ondansetron for vomiting within the first 24 h postoperatively, at 4 mg i.v. [86]. There was a trend to effectiveness at 8 mg i.v., but this effect was not statistically significant.

Ondansetron has been compared against other individual antiemetic drugs in addition to placebo. In a meta-analysis [87] of 23 RCTs with 3863 patients comparing ondansetron with droperidol, and 19 RCTs of 2502 patients comparing ondansetron with metoclopramide, the pooled odds ratio (95% CI) for prevention of vomiting were 0.70 (0.52 to 0.94) and 0.43 (0.31 to 0.61), respectively. The corresponding odds ratios (95% CI) for prevention of nausea were 0.99 (0.66 to 1.47) and 0.70 (0.45 to 1.10), demonstrating that ondansetron was significantly more effective than either droperidol or metoclopramide in preventing vomiting, but not nausea. Doses of all drugs varied: ondansetron 4 to 8 mg, and 0.10 mg·kg<sup>-1</sup> to 0.15 mg·kg<sup>-1</sup>; droperidol 0.625 mg to 2.5 mg, and 20 µg·kg<sup>-1</sup> to 75 µg·kg<sup>-1</sup>; metoclopramide 10 mg, and 0.25 mg·kg<sup>-1</sup> to 0.5 mg·kg<sup>-1</sup>. This mixed effectiveness of ondansetron over droperidol contrasts with another quantitative systematic review, in which data in adults from 20 RCTs showed that the odds ratio (95% CI) was 0.56 (0.41 to 0.76) and NNT (95% CI) was 12 (7.32) in favor of ondansetron over droperidol. Data on doses used were not available for assessment [88].

The role of ondansetron lies not only in the prevention of PONV but also in the treatment of established PONV. In a quantitative systematic review [89] of seven RCTs, it was shown that intravenous ondansetron was effective compared with placebo for the treatment of established early and late PONV. For the treatment of early PONV, the NNT values (95% CI) were 3.8 (2.6 to 6.6), 3.2 (2.3 to 5.2), and 3.1 (2.4 to 4.5) with 1, 4, and

8 mg of ondansetron, respectively. The respective NNT values at the corresponding doses for the treatment of established late PONV were 4.8 (3.5 to 7.9), 3.9 (3.0 to 5.7), and 4.1 (3.1 to 6.2). Thus, at doses used clinically there is no additional benefit in using higher doses of ondansetron for the treatment of established PONV. These results contrast with the situation in which ondansetron was used for the prophylaxis of PONV, when increased effectiveness was demonstrated at higher doses.

#### *Dexamethasone*

Dexamethasone, in doses of 8 mg to 10 mg, and 1 to 1.5 mg·kg<sup>-1</sup>, has been evaluated in a quantitative systematic review [90]. Results from 15 placebo-controlled trials show that dexamethasone was effective for the prevention of early and late PONV. The NNT values (95% CI) for the prevention of early and late vomiting were 7.1 (4.5 to 18) and 3.8 (2.9 to 5.0), respectively, in data from children and adults. Data for nausea were available in adults but not children. The NNT values for early and late nausea were 5.0 (–21 to 2.2) and 4.3 (2.3 to 26). Analysis of other trials in this review showed that antiemetics, such as ondansetron 4 mg i.v., granisetron 3 mg i.v., and perphenazine 70 µg·kg<sup>-1</sup> were more effective than dexamethasone for the prevention of PONV.

Other issues with dexamethasone concern the dose and timing of administration. In a double-blind placebo-controlled RCT of females undergoing thyroidectomy it was found that the minimum effective dose for the prevention of PONV was dexamethasone 5 mg i.v., given at induction of anesthesia [91]. Furthermore, in an RCT of 120 females undergoing hysterectomy, 10 mg of dexamethasone, given after induction anesthesia, significantly reduced the incidence of PONV within the first 2 h postoperatively, compared with administration at the end of the procedure, and rescue antiemetic consumption was significantly reduced [92].

#### *Droperidol*

Droperidol is a butyrophenone that may cause dose-dependent sedation and drowsiness. Therefore, the main issue with its use concerns the minimum dose required to prevent PONV. In a systematic review [93], it was shown that 0.5 mg to 0.75 mg of droperidol was sufficient to prevent early nausea and that at least 1 mg to 1.25 mg was required for late nausea, in adults. For early vomiting, at least 1 mg to 1.25 mg i.v. of droperidol was required, compared with a lower dose of 0.5 mg to 0.75 mg i.v. for late vomiting, in adults. In children, there was a dose-dependent effect for early and late vomiting, and the relative risk was clearly in favor of droperidol compared with placebo, at doses of 50 µg·kg<sup>-1</sup> to 75 µg·kg<sup>-1</sup> compared with 10 µg·kg<sup>-1</sup> to 20 µg·kg<sup>-1</sup>.

### *Metoclopramide*

Metoclopramide is an antagonist at central dopaminergic receptors, central and peripheral 5HT<sub>2</sub> receptors, and peripheral 5HT<sub>1</sub> receptors. In a systematic review of 66 randomized placebo-controlled trials involving 6266 patients, no antiemetic effect was detected within 6 h postoperatively and at 48 h [94]. In adults, doses varied from 5 mg to 35 mg via i.v., i.m., oral and intranasal routes. In children, the doses were 0.1 mg·kg<sup>-1</sup> to 0.5 mg·kg<sup>-1</sup>, given i.v. in all but one trial. Adverse reactions, such as extrapyramidal symptoms, sedation, drowsiness, dizziness, vertigo, and headache were uncommon, even at higher doses of metoclopramide.

### *Combination antiemetic therapy*

Combination antiemetic therapy or "balanced antiemesis" [95] is another technique that some investigators have been studying for the prevention of PONV. Combinations of a 5HT<sub>3</sub> receptor antagonist (ondansetron 4 mg; granisetron 3 mg, or 20 µg·kg<sup>-1</sup> to 40 µg·kg<sup>-1</sup>) with either dexamethasone 8 mg [90] or cyclizine 50 mg i.v. [96] have been shown to exhibit increased effectiveness compared with the individual 5HT<sub>3</sub> antagonist. Pueyo et al. [97] compared a combination of intravenous ondansetron 4 mg and droperidol 3.75 mg with ondansetron 4 mg, and found increased effectiveness, although Bugedo et al. [98] found no advantages in a combination of ondansetron 4 mg and droperidol 2.5 mg compared with ondansetron 4 mg. In a meta-analysis of RCTs, combinations of droperidol and a 5HT<sub>3</sub> antagonist did not have any significant advantages compared with individual agents [99].

Combination antiemetic therapy for PONV involving the administration of 200 mg of the oral NK-1 antagonist, CP1222721, and 4 mg i.v. of ondansetron has been compared with the individual drugs in a double-blind RCT [83]. There was a significant improvement in the median emesis-free time for 75% of patients in the combination group compared with the findings in the patients receiving CP1222721 or ondansetron separately. While there was no significant difference in nausea scores between the three groups within 8 and 24 h. The incidence of emesis within 24 h was significantly less with the combination compared with ondansetron but not with CP1222721. Another NK-1 antagonist has been assessed recently in patients receiving chemotherapy. The addition of the NK-1 antagonist, L754030, 300 to 400 mg, to granisetron 10 µg·kg<sup>-1</sup> i.v. and dexamethasone 20 mg orally was found to produce significant antiemetic benefits [100].

In summary, it appears that combination therapy involving the addition of some agents, such as dexamethasone, cyclizine, or an NK1 antagonist, to a 5HT<sub>3</sub>

antagonist provides additional prophylaxis against PONV compared with the individual 5HT<sub>3</sub> antagonist.

### *Prophylactic antiemetics during PCA opioids*

The effectiveness of administering an antiemetic to an opioid via a PCA device has been assessed in a quantitative systematic review of 14 eligible RCTs of 1117 patients [101]. Morphine was used in all but one RCT. Of the various antiemetic agents, such as hyoscine, propofol, metoclopramide, clonidine, promethazine, droperidol, ondansetron, and tropisetron, the most frequently used were the latter three drugs. Although droperidol, with an NNT (95% CI) of 2.8 (2.1 to 3.9), was effective for the prevention of PONV, no dose-response effect could be identified. Ondansetron and tropisetron were administered in various doses, and both drugs were found to be effective for the prevention of PONV. Their respective NNTs (95% CI) were 2.9 (2.1 to 4.7) and 4.7 (3.0 to 11).

### *Acupuncture*

The effect of the stimulation of the P6 acupuncture point on PONV was assessed in a meta-analysis of 19 RCTs involving 1679 patients undergoing tonsillectomy, laparoscopy, cesarean section, and gynecological and general surgery [102]. The acupuncture varied in terms of the type used, and its method, timing, and duration of administration. Manual acupuncture, electroacupuncture, transcutaneous electrical stimulation, and acupressure to P6 were given preoperatively, intraoperatively, and postoperatively, depending on the trial. In addition, the duration of treatment varied from 5 min to 7 days. It was found that this nonpharmacological technique had significant benefit compared with no treatment or sham treatment in adults for preventing nausea and vomiting, within 6 h. For early nausea, therefore, the relative risk (RR) (95% CI) was 0.34 (0.20 to 0.58) with an NNT (95% CI) of 4 (3 to 6). For early vomiting, the RR was 0.47 (0.34–0.64) and the NNT was 5 (4–8). There was no treatment benefit for late vomiting (0–48 h) in adults, or for early and late vomiting in children. In seven trials within this meta-analysis, stimulation of P6 and antiemetics (metoclopramide, cyclizine, droperidol) were compared, and it was found that there was no significant difference between these techniques in the prevention of early and late vomiting in adults.

### *Scoring systems*

In making a decision on whether to provide therapy to prevent the occurrence of PONV, assessment of factors that predict its occurrence is required. An ideal scoring system would be highly discriminative for all types of patients undergoing all forms of surgery, in any hospital,

and be easy to apply. Some scoring systems have identified predictive factors by logistic regression analysis, and, to use such forms of evaluation, the physician must take into account the different weighting of each factor [103]. However, a simplified scoring, based on four risk factors of equal weighting, has been evaluated in orthopedic, ophthalmic, otolaryngological, and general surgical patients. These factors comprised: female sex, history of motion sickness or PONV, nonsmoking, and use of intraoperative opioids. The ability of this scoring system to discriminate between patients who would and would not have PONV has been quantified by the area under the receiver operator curve, a plot of the true-positive rate against the false-positive rate. For a variety of operations, it was found that, in the presence of none, one, two, three, and four risk factors, the incidence of PONV was 10%, 21%, 39%, 61%, and 79% respectively [104]. In making a decision on whether to administer medication for the prevention of PONV, the use of such a simple scoring system would be helpful to the anesthesiologist.

#### Postoperative gastrointestinal motility

Ileus is a common problem occurring after major surgery and is caused by lack of motility of the left side of the colon. Its occurrence can delay the absorption of enteral nutrition and drugs, in addition to causing abdominal distension, patient discomfort, and prolonged hospital stay. Factors that have been shown to inhibit gastrointestinal motility include sympathetic reflexes and also  $\mu$  receptor agonists, nitric oxide, substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and corticotrophin-releasing factor [105]. There is experimental evidence in rats that  $\kappa$  opioid receptor agonists reverse the inhibition of gastrointestinal transit, in a dose-dependent fashion [106]. However, the administration of metoclopramide, cisapride, [107] and erythromycin [108] has not been found to be effective for the treatment of postoperative ileus.

Inhalation agents [77] and opioids [109] used in the intraoperative period for abdominal surgery cause a reduction in gastrointestinal motility. In addition, the type of analgesia employed in the postoperative period is a critical factor that affects the return of normal gastrointestinal motility. In current anesthetic practice, the main options available for providing postoperative analgesia for major abdominal surgery are systemic opioids and epidural analgesia. In a review of 16 studies, of which 10 were RCTs, it has been clearly demonstrated that return of gastrointestinal motility occurred earlier in patients who had epidural analgesia compared with findings in those who had systemic opioids [110]. In these studies, a variety of end points were used, such as

time to first bowel sounds, time to first passing of flatus or feces, transit time of radio-opaque markers, and barium transit time. In addition, in three RCTs, it was found that return of gastrointestinal motility was delayed in patients receiving thoracic epidural morphine compared with findings in those receiving thoracic epidural bupivacaine for postoperative analgesia [110]. It is believed that the effectiveness of thoracic epidurals occurs because of blockade of inhibitory thoracolumbar sympathetic efferents, allowing unopposed parasympathetic activity via craniosacral efferents. In addition, there is blockade of nociceptive afferent neural impulses, decreased levels of endogenous circulating catecholamines, and a reduction in the administration of opioids. Despite some lack of evidence for efficacy in postoperative ileus [111], it is currently believed that epidural analgesia should be used as part of a multimodal care pathway of early nutrition, early mobilization [112], and minimally invasive surgery that facilitates postoperative recovery and minimizes morbidity and duration of hospital stay [113]. In addition there is clinical evidence that postoperative ileus following colorectal resection may be minimized by laparoscopic techniques compared with conventional surgery [114].

#### Effect of postoperative analgesia on anastomotic leakage following colorectal surgery

The etiology of anastomotic leakage following colorectal surgery includes patient factors, such as anemia and comorbidity; surgical factors, such as bowel preparation and operative expertise; and factors related to anesthesia and pain management. For anesthesiologists, the key clinical question is whether there is a relationship between postoperative analgesia and the development of anastomotic leakage. In this section, issues concerning the administration of systemic morphine vs systemic pethidine, in addition to epidural analgesia vs systemic opioid analgesia are examined.

#### Systemic morphine vs systemic pethidine analgesia

There has been controversy on whether or not the type of opioid used for postoperative analgesia affects the incidence of anastomotic dehiscence. Early studies [115,116], in which morphine and pethidine were administered by the i.m. route on demand, suggested that the incidence of anastomotic dehiscence was more common in patients who received morphine compared with those who received pethidine. Intravenous or intramuscular morphine has been shown to double the frequency of colonic contractions [117] and to increase intraluminal pressure, especially in diverticular disease [118]. Pethidine, on the other hand, is associated with

decreased colonic intraluminal pressure [118], and so there seems to be some theoretical grounds supporting these clinical findings. However, in a recent trial in which equianalgesic doses of PCA morphine or PCA pethidine by the i.v. route were compared, it was found that there was no significant difference in the incidence of anastomotic breakdown [119]. This finding may be explained on the basis that, in the earlier studies, the use of i.m. morphine would have been associated with higher peak plasma concentrations of the drug than those occurring with the i.v. PCA method of administration, and, consequently, with this PCA method, there may be a reduced tendency to the formation of contraction rings.

#### *Epidural analgesia vs systemic opioid analgesia*

It has been speculated previously that epidural analgesia would be likely to increase the risk of anastomotic leakage following colorectal surgery, because of increased intestinal motility and intraluminal pressure, in addition to possible reduced anastomotic blood supply. This issue has been examined in a review of RCTs from 1966 to 2000, available on Medline [120]. In 11 RCTs of this review, epidural local anesthetic, with and without opioids, was compared with systemic opioids. Although the incidence of anastomotic leakage was 16/255 for epidurals compared with 9/252 for systemic opioids, there was no statistically significant difference. In addition, data from 3 RCTs of this review comparing pure epidural opioid with epidural local anesthetic with and without an opioid did not demonstrate a significantly increased risk of anastomotic leakage with the type of drugs administered.

#### **Alternative routes of drug administration**

Gastrointestinal dysfunction impairs reliable drug absorption via the oral route, and in the immediate postoperative period after major surgery, it is mandatory to avoid oral administration of opioids for postoperative pain relief until it is clear that bowel motility has returned to normal. Otherwise, multiple doses which are not absorbed may be dumped suddenly into the upper GI tract when motility returns, leading to acute toxicity [121]. The presence of intestinal obstruction, abdominal pain, and PONV are common situations in which other methods of drug administration become necessary. In many instances, intravenous access is the standard alternative route. However, in specific situations, such as minor procedures or situations in which intravenous access can prolong hospital stay, other routes of drug administration would be highly desirable. In anesthetic practice, the administration of analgesics and sedative

agents by intranasal, oral mucosal, transdermal, and rectal routes has been evaluated.

#### *Intranasal route*

The nasal mucosa has a rich blood supply, allowing rapid absorption of some drugs. For example, under optimal conditions, the administration of midazolam via the nasal mucosa may lead to rapid and almost complete absorption. In a study of 14 adult patients with neither rhinitis nor nasal obstruction, time (SD) to peak arterial concentration of midazolam was 14 (2) min after the administration of midazolam  $0.15 \text{ mg} \cdot \text{kg}^{-1}$  by nasal spray. Bioavailability (SD) was 83 (15) % with minimal hydroxymidazolam concentrations, indicating minimal first-pass metabolism from the swallowed drug [122]. However, despite these favorable pharmacokinetics, in a study of 44 children given intranasal midazolam  $0.2 \text{ mg} \cdot \text{kg}^{-1}$ , Griffith et al. [123] did not recommend this route for premedication because of the unpleasant taste, and the complaints of stinging and crying.

The irritant effects observed with midazolam do not seem to occur with intranasal opioids [124]. In a recent study of patients with cancer pain it was found that intranasal fentanyl  $20 \mu\text{g}$ , administered by spray, was tolerable and provided additional analgesia within 10 min [125]. In healthy volunteers [126], intranasal fentanyl  $54 \mu\text{g}$  produced a maximum concentration within 5 min and a bioavailability of 71 %. Although the nose is not the standard route for the administration of analgesics, there are plans to introduce a patient-controlled intranasal device [127].

Intranasal oxycodone has also been investigated recently in volunteers. It was found that with alternate sprays of 0.1 ml to each nostril, to a maximum dose of  $0.1 \text{ mg} \cdot \text{kg}^{-1}$ , the values for mean time (95% CI) to peak concentration and bioavailability (95% CI) were 25 (20–240) min and 0.46 (0.25–0.67), respectively. Although oxycodone was absorbed rapidly, there were large inter-individual differences, suggesting that careful titration would be required to avoid adverse effects [128].

#### *Oral mucosal route*

Within the oral cavity, the sublingual and buccal mucosa are the main sites for drug absorption. Both sites are nonkeratinized, but the buccal mucosa is thicker, relatively immobile, and less permeable than the sublingual mucosa. The sublingual mucosa is relatively mobile and is constantly washed by saliva. Thus, the sublingual route would be appropriate for rapid but infrequent drug delivery, whereas the buccal route is better suited for sustained drug delivery [129].

Of the analgesic drugs administered via the buccal route, fentanyl has been studied in greatest detail. Oral

transmucosal fentanyl has been advocated as a useful non-invasive method of providing analgesia for children undergoing painful procedures. In a clinical trial of 48 children receiving a lollipop of fentanyl 15 to 20  $\mu\text{g}\cdot\text{kg}^{-1}$ , Schechter et al. [130] found that pain scores were significantly less during bone marrow aspiration or lumbar puncture performed 30 min after the lollipop was given. In another trial, in which oral transmucosal fentanyl 10 to 15  $\mu\text{g}\cdot\text{kg}^{-1}$  was given to children aged 2 to 10 years, there was no evidence of improved cooperation at induction of anesthesia compared with the placebo group. Although patients receiving fentanyl were more sedated than those in the placebo group, there was no vomiting or desaturation in the preoperative period. From pharmacokinetic measurements, the bioavailability was 0.33 [131].

The effects of fentanyl administered via the oral transmucosal route have also been evaluated in healthy adult volunteers. With 800  $\mu\text{g}$  of fentanyl consumed over 15 min, the median time (95% CI) to maximum concentration was approximately 24 (20 to 71) min, and the bioavailability (SE) was estimated to be 40 (11)% [132]. In addition, after three doses, at 6-h intervals, there was no evidence of significant changes in pharmacokinetics, suggesting that alterations in drug prescribing are not required when multiple doses of transmucosal fentanyl are used [132]. Dose-proportional pharmacokinetics are observed with oral transmucosal fentanyl, i.e., with increases in dose administered, there are proportional increases in maximum concentration, area under the concentration time curve, and adverse effects, such as respiratory depression [133].

In addition to opioids, the oral mucosal administrations of antiemetics and sedatives has been studied. Buccal prochlorperazine, at a dose of 6 mg, was found to be effective in preventing PONV in patients receiving PCA morphine after abdominal hysterectomy [134]. In a study of buccal midazolam 10 mg in 2 ml for 5 min in adult volunteers, it was found that, although time ( $\pm 2$  SD) to maximum venous concentration was 48 (28) min, electroencephalography (EEG) effects were evident within 5 min of administration [135]. In a placebo-controlled RCT [136] in children (aged 12 to 129 months) of sublingual midazolam in thick grape syrup, satisfactory sedation was evident in 52% and 64%, 15 min after 0.5  $\text{mg}\cdot\text{kg}^{-1}$  and 0.75  $\text{mg}\cdot\text{kg}^{-1}$ , respectively.

#### *Transdermal route*

In anesthetic practice, the transdermal route has been utilized mainly for the management of chronic pain. This route is particularly helpful for patients with cancer pain or chronic pancreatitis [137], when nausea, vomiting, and dysphagia may preclude oral drug administration.

However, owing to its protective barrier functions, and variations in structure and perfusion, the skin does present an obstacle to rapid reliable drug administration. Of all analgesics, fentanyl has been evaluated extensively and may be used to illustrate the pharmacokinetics of the transdermal route.

Transdermal therapeutic systems (TTS) of fentanyl consist of fentanyl dissolved in an enhancer of ethanol and a rate-controlling membrane of ethylene-vinyl acetate. Ethanol extracts lipids in the stratum corneum [138] and, hence, helps to achieve the target drug delivery rate. Variations in skin permeation are minimized by the rate-controlling membrane [139]. The rate of administration is proportional to the surface area of drug exposed to skin, and current patches can deliver fentanyl at rates of 25, 50, 75, and 100  $\mu\text{g}\cdot\text{h}^{-1}$ . The onset time for this route of administration is prolonged, and is reflected in the 17 to 48 h taken to reach maximum plasma concentration [140].

Age has no significant effect on the pharmacokinetics of TTS fentanyl. In a study of a transdermal patch delivering fentanyl at 50  $\mu\text{g}\cdot\text{h}^{-1}$  for 72 h, it was found that the time to maximum plasma concentrations, elimination half-life, and area under the time concentration curve did not differ significantly between elderly and young adults [141]. In children aged 18 to 60 months, time (SD) to reach maximum concentration was 18 (11) h with a patch designed to release fentanyl at 25  $\mu\text{g}\cdot\text{h}^{-1}$  for 72 h. As would be expected, maximal fentanyl concentrations were higher in younger children [142].

The use of fentanyl delivered via the TTS is associated with delayed analgesic action, and the TTS is therefore unsuitable for acute pain management. However, it has been possible to enhance transdermal administration by iontophoresis, in which the transport of an ionisable drug is facilitated by an external electric field [143]. A PCA electrotransport therapeutic system (ETS) for fentanyl has been developed, delivering 80 boluses of 40  $\mu\text{g}$ . Each bolus is administered over 10 min. In a clinical trial of 174 patients, it was found that ETS fentanyl seemed to provide satisfactory analgesia for acute pain after orthopedic and gynecological surgery [144].

Although TTS fentanyl has not been recommended for acute pain, transdermal ketamine has been found recently to be an effective adjuvant after abdominal gynecological surgery, when given at a rate of 25 mg per 24 h, without associated hallucinations or nightmares [145].

#### *Rectal route*

Rectal drug administration is particularly useful when the oral route cannot be used. Recently, a new prepara-

tion of 30-mg morphine suppositories, given twice daily for 5 days in patients with cancer, was reported to provide analgesia equivalent to the same oral dose [146]. In comparison with results with the oral morphine, the rectal route was associated with a higher bioavailability of morphine and lower plasma concentrations of morphine-6-glucuronide and morphine-3-glucuronide, indicating reduced first-pass metabolism with rectal administration. Median time (range) to maximum plasma concentrations after the rectal administration of morphine was 4 (0–6) h.

The rectal route has been used extensively by anesthesiologists for the treatment of pain with simple analgesics. In one study, involving children aged 9 weeks to 11 years, 25 mg·kg<sup>-1</sup> of paracetamol, given rectally at 6-h intervals for 5 days, was shown to be safe, with no evidence of supratherapeutic concentrations [147]. The mean time (SD) to reach maximum concentration in the first dosing interval was 2.37 (1.10) h. In adults, a higher single dose of rectal paracetamol, of 40 µg·kg<sup>-1</sup>, did not provide increased analgesia compared with the lower dose of 20 µg·kg<sup>-1</sup>, following vaginal or abdominal hysterectomy. Although the maximum plasma concentration of paracetamol was significantly greater with the higher dose of paracetamol, there was no significant difference in the time taken to reach this concentration. The mean times (SD) to reach maximum concentration were 4.2 (1.7) h and 3.6 (1.4) h for the higher and lower paracetamol doses, respectively [148].

Diclofenac suppositories are commonly used in acute and chronic pain management. In healthy male volunteers, it was found that 50 mg of rectal diclofenac exhibited a slightly increased bioavailability compared with that shown with the oral form. In addition, time to maximum plasma concentration for the rectal route was shorter, taking  $0.62 \pm 0.06$  h compared with  $1.58 \pm 0.06$  h for the oral route [149].

## Conclusion

In the perioperative period, impairment of gastrointestinal function can occur, causing increased morbidity and delayed recovery. Current evidence for the optimal management of gastroesophageal reflux and aspiration of gastric contents, PONV, gastrointestinal ileus, and anastomotic leakage, as well as alternative routes of drug administration, have been discussed. Careful consideration of these factors and the application of appropriate treatments will go a long way to help our patients recover from surgery and anesthesia.

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### **7.3. Editorial**

An editorial concerning administration of local anaesthetics into the peritoneal cavity was published in the British Journal of Anaesthesia. This editorial forms part of the background of my thesis.

Ng A, Smith G. Intraperitoneal administration of analgesia: is this practice of any utility? Br J Anaesth 2002;89:535-7.

BJA

*"I would have everie man write what he knowes and no more."—Montaigne*  
**BRITISH JOURNAL OF ANAESTHESIA**

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**Editorial I**

**Intraperitoneal administration of analgesia: is this practice of any utility?**

Local anaesthetic techniques are part of the multimodal approach to postoperative pain management.<sup>1</sup> This involves the use of opioids, non-steroidal anti-inflammatory drugs (NSAIDs)<sup>2</sup>, paracetamol<sup>3</sup> and local anaesthetics.<sup>4</sup> The purpose of this editorial is to review whether or not instillation of local anaesthetics into the peritoneal cavity is a worthwhile modality in routine clinical practice during some intra-abdominal procedures.

Data from a nationwide survey in the UK of anaesthesia for gynaecological laparoscopy revealed that local anaesthetic solutions are administered commonly, particularly into the wound and the peritoneal cavity.<sup>5</sup> For this type of ambulatory surgery and anaesthesia, the main advantage of using local anaesthetics is that they do not have the adverse effects of opioids, which may delay recovery and discharge from hospital. These effects include postoperative nausea, sedation,<sup>2</sup> impairment of return of gastrointestinal motility, and pruritis. In addition, time to return of bowel function in the postoperative period may be reduced when the use of opioids is obviated by administering local anaesthetics.<sup>6</sup>

Although NSAIDs provide morphine-sparing effects<sup>2</sup>, they do not appear, on their own, to provide sufficiently reliable postoperative analgesia for minimally invasive laparoscopic surgery.<sup>7</sup> In addition, they have the disadvantage that they may cause gastric irritation in addition to impairing platelet and renal function. In the perioperative period, many patients are at risk of these problems because of enforced starvation, dehydration and tissue trauma. Additional methods of analgesia are thus necessary.

Local anaesthetics have been administered into the peritoneal cavity during minimally invasive procedures, such as laparoscopic cholecystectomy and gynaecological laparoscopy for sterilization and diagnosis,<sup>8</sup> in addition to open abdominal procedures, such as total abdominal hysterectomy.<sup>4, 9, 10</sup> The rationale for this route of administration is that the peritoneum is exposed to block of visceral nociceptive conduction, thereby providing an additional mechanism of analgesia. However, absorption from the large peritoneal surface may also occur, and this may be a further mechanism of analgesia.

It has been shown after radical retropubic prostatectomy that i.v. lidocaine 1.5 mg kg<sup>-1</sup> bolus and 2–3 mg min<sup>-1</sup> infusion reduced morphine consumption and total pain

scores significantly compared with placebo.<sup>6</sup> These data are supported by a clinical trial in which i.v. lidocaine produced a concentration-dependent reduction in pain scores when the plasma concentration exceeded 1.5 µg ml<sup>-1</sup>.<sup>11</sup> In addition, it has been shown in rats that administration of systemic lidocaine may suppress peripheral ectopic impulse discharge<sup>12</sup> and inhibit central excitatory responses to glutamate.<sup>13</sup> With bupivacaine, the range of mean plasma concentration (0.92–1.14 µg ml<sup>-1</sup>) after intraperitoneal instillation of plain bupivacaine 100–150 mg<sup>14–16</sup> is well below the toxic concentration of 3 µg ml<sup>-1</sup>.<sup>17</sup> Similar systemic concentrations have produced neurological symptoms, such as paraesthesia, tingling and perioral numbness, in unanaesthetized volunteers during i.v. infusions of bupivacaine.<sup>18, 19</sup> However, it remains unclear whether these concentrations produce a measurable postoperative analgesic effect.

Although laparoscopic cholecystectomy is a minimally invasive procedure, it is associated with intra-abdominal, incisional and shoulder pain after surgery.<sup>20</sup> Many clinical trials have been carried out to assess if intraperitoneal instillation of local anaesthetics to the gall bladder bed and right subdiaphragmatic space has produced any analgesic effect. Of 13 clinical trials in a systematic review<sup>8</sup> of intraperitoneal administration of bupivacaine 50–200 mg in volumes of 10–100 ml, significant reduction in overall pain occurred in seven trials but not in the other six. In addition, supplementary analgesic consumption was reduced significantly in five trials. This systematic review of bupivacaine concurs with a subsequent clinical trial in which intraperitoneal lidocaine 200 mg in 200 ml instilled under the right diaphragmatic surface increased time to first analgesia from 25 to 105 min after laparoscopic cholecystectomy.<sup>21</sup> Interestingly, in a recent study, an intraperitoneal combination of local anaesthetic and NSAID was shown to be more effective in reducing pain scores and opioid consumption than either placebo or intraperitoneal local anaesthetic with i.v. NSAID. Analgesic effects were greater in patients who had intraperitoneal lidocaine 200 mg with intraperitoneal tenoxicam 20 mg diluted to 200 ml compared with either placebo or intraperitoneal lidocaine 200 mg in 200 ml with i.v. tenoxicam 20 mg.<sup>22</sup> Thus it would appear that, for laparoscopic cholecystectomy,

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intraperitoneal local anaesthetic solutions produce a modest analgesic effect which may not be adequate for routine analgesia.

Clinical trials of intraperitoneal instillation of local anaesthetics during gynaecological laparoscopy appear to demonstrate more effective analgesia, possibly because this operation is less traumatic than laparoscopic cholecystectomy.<sup>8</sup> In a systematic review of bupivacaine or etidocaine dripped onto the Fallopian tubes during laparoscopic sterilization under general anaesthesia, pain scores and supplementary analgesic consumption were reduced significantly for up to 2 h after surgery. Furthermore, intraperitoneal lidocaine, infiltrated into the mesosalpinx or into the Fallopian tubes, or coating Filshie clips, produced similar analgesic effects.<sup>8</sup> This has been confirmed in awake postpartum patients when intraperitoneal 0.5% lidocaine 80 ml reduced the need for supplementary fentanyl, ketamine and rescue general anaesthesia during tubal ligation.<sup>23</sup> In addition, intraperitoneal instillation of ropivacaine 150 mg during gynaecological laparoscopy produced a statistically significant 24 h morphine-sparing effect compared with placebo.<sup>24</sup>

The intraperitoneal cavity appears also to be an effective route for postoperative analgesia after administration of local anaesthetic in combination with an opioid. In a clinical trial of 100 patients undergoing laparoscopic tubal ligation, pain scores at rest and on movement were significantly lower in patients who had a combination of intraperitoneal meperidine 50 mg and intraperitoneal 0.125% bupivacaine 80 ml with epinephrine 1:200 000 compared with those who had a combination of i.m. meperidine 50 mg and intraperitoneal 0.125% bupivacaine 80 ml with epinephrine 1:200 000.<sup>25</sup>

In summary, it seems that intraperitoneal instillation of local anaesthetics is effective for gynaecological laparoscopy but may not be so for laparoscopic cholecystectomy.<sup>8</sup> Laparoscopic cholecystectomy is a longer procedure with greater tissue dissection than gynaecological laparoscopy. Recent evidence suggests that instillation of local anaesthetics both into the peritoneum and into the incision may be required after laparoscopic cholecystectomy. Instillation of ropivacaine 286 mg in 66 ml in this way during laparoscopic cholecystectomy produced lower pain scores and reduced morphine requirements compared with placebo.<sup>26</sup>

While intraperitoneal local anaesthetics have produced analgesic effects after gynaecological laparoscopy, they have not done so after total abdominal hysterectomy via a Pfannenstiel incision.<sup>9, 10</sup> Intraperitoneal instillation of either 0.5% bupivacaine 20 ml with epinephrine 1:200 000 diluted to 50 ml with normal saline or 2% lidocaine 20 ml with epinephrine 1:200 000 diluted to 50 ml with normal saline did not demonstrate any opioid-sparing effects compared with placebo.<sup>10</sup> It is likely that while intraperitoneal local anaesthetics may block visceral nociceptive conduction after minimally invasive surgery such as gynaecological laparoscopy, they do not block

afferent nociceptive transmission from cutaneous sites. It appears that a combination of intraperitoneal and incisional administration of local anaesthetics is required after open abdominal procedures. Epinephrine 5 µg ml<sup>-1</sup> with 0.25% bupivacaine 30 and 20 ml administered into the peritoneum and incision respectively produced morphine-sparing analgesia for 4 h after total abdominal hysterectomy via a Pfannenstiel incision.<sup>4</sup>

The difference in outcome of studies on intraperitoneal instillation of local anaesthetics may result from the type of surgery and the location, dose, type and timing of instillation. The failure in some studies to show an analgesic effect may result from rapid dilution of local anaesthetic in the peritoneal cavity.<sup>27</sup> It is not possible, however, to increase the dose of local anaesthetic without increasing the risk of systemic toxicity. Although potentially more toxic than lidocaine, bupivacaine has the advantage that it has a longer duration of action. However, in clinical trials the analgesic effects of bupivacaine have been short-lived. It has been shown in a mouse model that intraperitoneal bupivacaine in a liposomal formulation may prolong the duration of action and also reduce the possibility of systemic toxicity.<sup>28</sup> An alternative is levobupivacaine, the *S*(-) enantiomer of bupivacaine, the analgesic effects and duration of which are thought to be similar to those of racemic bupivacaine but with a reduced risk of systemic toxicity<sup>29</sup>, thus allowing administration of a larger and more potent dose.

The intraperitoneal route of administration of local anaesthetic is simple: it does not involve additional central neural axial block and is particularly suited to the practice of ambulatory anaesthesia. However, for this route to be useful as a routine for pain management during all forms of minimally invasive surgery, it must not be limited by the dose of local anaesthetic. Thus the search goes on for newer, less toxic local anaesthetics that have a longer duration of action. It is hoped that this development may lead ultimately to improvements in convalescence and to a reduction in the risk of hospital readmission after minimally invasive surgery.

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#### **7.4. Original articles**

So far, four main articles have published as a result of the work done for this thesis.

They are as follows:

Ng A, Swami A, Smith G, Davidson AC, Emembolu J. The analgesic effects of intraperitoneal and incisional bupivacaine with epinephrine following total abdominal hysterectomy. *Anesth Analg* 2002; 95:158-62.

Ng A, Habib A, Swami A, Smith G, Davidson AC. Prospective randomised double blind placebo controlled clinical trial investigating the effect of transcervical papaverine and bupivacaine on postoperative analgesic requirements following laparoscopic application of Filshie clips. *Eur J Anaesthesiol* 2002;19:803-7.

Ng A, Parker J, Toogood L, Cotton BR, Smith G. Does the opioid-sparing effects of rectal diclofenac following total abdominal hysterectomy benefit the patient? *Br J Anaesth* 2002;88:714-6.

Ng A, Smith G, Davidson AC. Analgesic effects of parecoxib following total abdominal hysterectomy. *Br J Anaesth* 2003;90:746-9.

# The Analgesic Effects of Intraperitoneal and Incisional Bupivacaine With Epinephrine After Total Abdominal Hysterectomy

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The objective of our study was to see if incisional and intraperitoneal bupivacaine with epinephrine produces analgesia after total abdominal hysterectomy. Forty-six ASA physical status I and II patients received a standardized anesthetic, patient-controlled analgesia (PCA) morphine, and rectal paracetamol 1 g every 6 h. Patients were randomized to receive 50 mL of bupivacaine 0.25% with epinephrine 5 µg/mL or 50 mL of normal saline. Thirty milliliters and 20 mL of treatment solution were administered into the peritoneum and incision, respectively, before wound closure. Seventeen and 16 patients in the Placebo and Bupivacaine groups, respectively, completed the study. The reasons for withdrawal were PCA malfunction, PCA discontinued too early, nausea, chest infection, intraabdominal drain insertion, and protocol violation.

There were no significant differences between the Bupivacaine and Placebo groups in age, height, weight, or duration of surgery. Pain on movement was significantly more intense in the Placebo group than in the Bupivacaine group on awakening. Morphine consumption (interquartile range) over 24 h was 62 mg (53–85 mg) in the Placebo group compared with 44 mg (33–56 mg) in the Bupivacaine group ( $P < 0.01$ ). This significant difference was attributable to the larger morphine consumption in the Placebo group in the first 4 postoperative h. We conclude that a combination of intraperitoneal and incisional bupivacaine with epinephrine provides significant morphine-sparing analgesia for 4 h after total abdominal hysterectomy.

(Anesth Analg 2002;95:●●●—●●●)

**A**t our institution, morphine administered via a patient-controlled analgesic (PCA) device is the current standard for the provision of postoperative analgesia after total abdominal hysterectomy (TAH). Patients usually require PCA for at least 24 h, after which they receive oral analgesic drugs. Although PCA morphine provides satisfactory analgesia, it is associated with adverse effects, such as sedation, nausea, and vomiting (1,2). Other methods of analgesia that have morphine-sparing effects are therefore frequently used to reduce postoperative morbidity.

Previously presented by A. Ng at the Anesthesia Research Society, Nottingham, United Kingdom, November 23, 2001. The abstract from this meeting will be published in the British Journal of Anesthesia.

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In clinical trials of patients undergoing TAH, the administration of bupivacaine into the abdominal wall (3–5) or the peritoneal cavity (6) during surgery has not been found to result in reduced postoperative morphine consumption compared with placebo. Whereas intraperitoneal local anesthetics may block afferent nociceptive transmission from visceral structures, they do not block conduction from cutaneous sites. Similarly, incisional local anesthetics may block nociceptive conduction from cutaneous sites but would not be expected to block conduction from visceral areas of surgery. Consequently, the failure to demonstrate beneficial effects after either an incisional or intraperitoneal administration of local anesthetics during TAH may be attributable to the hypothesis that nociceptive transmission needs to be blocked from both cutaneous and visceral sites. The objective of the present investigation was to determine whether the administration of local anesthetics into both visceral and cutaneous areas of surgery produces measurable analgesia after TAH.

## Methods

After obtaining local institutional Research Ethics Committee approval and informed patient consent, we recruited 46 ASA physical status I and II patients, aged 20–65 yr, undergoing TAH. Patients were excluded if TAH was scheduled for malignancy or if there was a history of chronic pain, continuous use of analgesic drugs, or inability to use the PCA device.

All patients received a standardized anesthetic technique with propofol 2–4 mg/kg, a nondepolarizing muscle relaxant, morphine 10 mg IV, and ondansetron 4 mg IV. Their lungs were ventilated with nitrous oxide and isoflurane 1%–1.5% in oxygen via a cuffed tracheal tube. At the end of the procedure, residual neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. For postoperative analgesia, patients received PCA morphine and rectal paracetamol 1 g after the induction and subsequently at 6-h intervals.

Patients were allocated randomly to receive either 50 mL of bupivacaine 0.25% with epinephrine 5 µg/mL (Bupivacaine group) or 50 mL of normal saline (Placebo group). Before wound closure, 30 mL and 20 mL of the appropriate treatment solution were administered into the peritoneal cavity and abdominal wall, respectively. The surgeon who was blinded to the treatment was asked to infiltrate all layers of the abdominal wall during closure, including muscle and cutaneous layers.

In the postoperative period, assessments were made on awakening and at 8, 12, and 24 h by a member of the staff blinded to the treatment. Pain at rest and on movement (induced by sitting) was assessed on a visual analog scale (0–100 mm). Sedation was assessed using a categorical scale of 0 for an alert patient, 1 for an occasionally drowsy but easy to arouse patient, 2 for a frequently drowsy but easy to arouse patient, 3 for a severely drowsy and difficult to arouse patient, and 4 for normal sleep. In addition, postoperative nausea and vomiting were assessed on a categorical scale comprising 0 for none, 1 for nausea, 2 for vomiting on one occasion, and 3 for vomiting on more than one occasion. The PCA device recorded morphine consumption.

From a previous study on incisional infiltration of bupivacaine with epinephrine in our department (3), we considered that to have an 80% chance of detecting a 35% reduction in 24-h morphine consumption at the 5% significance level, 22 patients per group would be required. Data were processed in Excel 2000 (Microsoft, Bellevue, WA) and SPSS 9.5 (SPSS, Chicago, IL). Data were analyzed using analysis of variance with repeated measures,  $\chi^2$  test, unpaired *t*-test, and Mann-Whitney test, as appropriate.  $P < 0.05$  was considered to be statistically significant.

## Results

Of 46 patients, 13 did not complete the study because of the following reasons: PCA malfunction, PCA discontinued too early, nausea, chest infection, intraabdominal drain insertion, and protocol violation. There were no significant differences in age, weight, or duration of surgery between the remaining patients (Table 1). However, there were significantly ( $P = 0.03$ ) more ASA physical status I and fewer ASA physical status II patients in the Bupivacaine group than in the Placebo group.

The median (interquartile range) morphine consumption was significantly ( $P < 0.01$ ) smaller in the Bupivacaine (44 mg [32–56 mg]) than in the Placebo group (62 mg [53–85 mg]) (Fig. 1). This significant difference was attributable largely to the reduction in morphine consumption within the first 4 postoperative h (Fig. 2).

On awakening, pain scores on movement, but not at rest, were significantly ( $P = 0.01$ ) less in the Bupivacaine group than in the Placebo group. However, at 8, 12, and 24 h, there was no difference in pain scores between the two groups (Table 2). With the exception of the low sedation score of 1 (0–2) in the Bupivacaine group and 0 (0–0) in the Placebo group at 24 h, there were no significant differences between the groups in sedation and nausea (Table 3).

## Discussion

We have found that a combination of incisional and intraperitoneal bupivacaine with epinephrine administered during TAH reduced 24-hour ( $P < 0.01$ ) morphine consumption significantly compared with placebo. This difference was attributed to a significant reduction in morphine consumption in the first four postoperative hours ( $P < 0.01$ ). The lack of a significant difference in morphine consumption beyond four hours (Fig. 2) is likely to be attributable to the metabolism of bupivacaine and, hence, loss of its local anesthetic effect. Because there was no trend in a difference in morphine consumption between the two groups beyond four hours, it is unlikely that a type II error has occurred. In the presence of a possible difference in morphine consumption, it would have been required to study additional patients to make up for the ones who were withdrawn from the study.

On awakening, pain scores on movement ( $P = 0.01$ ) were significantly less in the Bupivacaine group compared with the Placebo group. With the exception of the low sedation score of 1 (0–2) in the Bupivacaine group and 0 (0–0) in the Placebo group at 24 hours, there were no significant differences in sedation and nausea scores between the two groups. There were significantly ( $P = 0.03$ ) more ASA physical status I

Table 1. Baseline Characteristics

	Placebo group	Bupivacaine group
Age (yr)	42 (8)	42 (8)
Weight (kg)	67 (14)	66 (8)
ASA physical status I/II	8/9	14/2*
Duration of surgery (min)	65 (60-77)	63 (56-75)
Reasons for patient withdrawal		
Pump malfunction or discontinued early	3	0
Nausea, requesting withdrawal	1	1
Chest infection	0	1
Intraabdominal drain insertion	1	4
Protocol violation	1	1

Age and weight are expressed as mean (sd), and duration of surgery is expressed as median (interquartile range).

\*  $P = 0.03$ , significant difference.

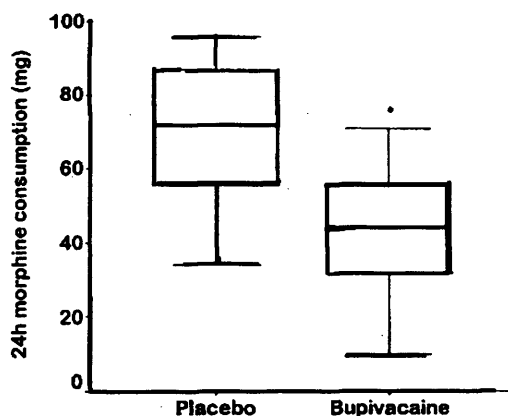


Figure 1. Twenty-four-hour morphine consumption. Data are expressed as median (interquartile range). \*Significant difference ( $P < 0.01$ ).

and fewer ASA physical status II patients in the Bupivacaine group than in the Placebo group. This difference was a consequence of the randomization process and is unlikely to affect the results because the patients were all moderately healthy.

Incisional local anesthetics provide analgesia in many clinical studies (7). However, in patients undergoing TAH, either an incisional (3-5) or intraperitoneal (6) administration of local anesthetics during surgery has not produced a demonstrable reduction in postoperative morphine consumption. These negative results contrast with postoperative patient-controlled incisional instillation of local anesthetics after TAH. In this study, in which bupivacaine 0.25% was administered to the wound through a catheter, postoperative opioid consumption, as well as the incidence of nausea, and ondansetron administration were significantly less in the Bupivacaine group compared with the Placebo group (8).

There have been many clinical studies of the use of intraoperative local anesthetics to see if they reduce

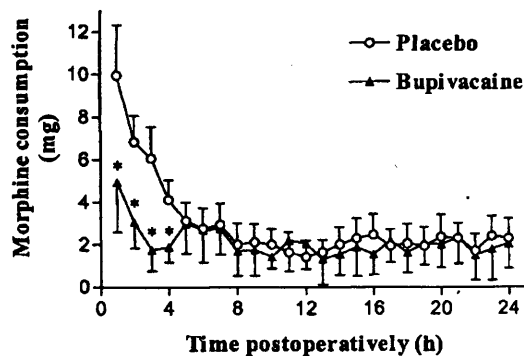


Figure 2. Hourly morphine consumption. Data are expressed as mean (95% confidence interval). \*Significant difference ( $P < 0.01$ ).

the need for postoperative analgesic medications. A qualitative systematic review (7) of the use of incisional local anesthetics for postoperative analgesia after abdominal operations showed that there was improved pain relief after inguinal herniotomy. For other types of surgery, such as TAH, open cholecystectomy, cesarean delivery, and major upper abdominal surgery, the evidence for the value of instillation of local anesthetics into the incision is equivocal.

The failure of some of the previous trials to show significant analgesic benefits may be attributable to the site of surgery, timing of the administration, and dose of the local anesthetic. In addition, it is possible that either incisional or intraperitoneal local anesthetics alone may not be adequate to produce measurable postoperative analgesia. Our data suggest that block of both visceral and somatic conduction is important if an analgesic-sparing effect is to be demonstrated after major surgery such as TAH.

Our results do not explain why only the incisional administration in the postoperative period by PCA (8) but not the incisional administration at the time of surgery (3) produces an opioid-sparing effect. Patients administering bupivacaine into their wound by PCA

Table 2. Pain Visual Analog Scores

Postoperative time (h)	Activity	Placebo group (mm)	Bupivacaine group (mm)
0	Rest	70 (50-80)	50 (28-62)
	Movement	80 (68-80)	50 (44-63)*
8	Rest	40 (27-56)	45 (29-53)
	Movement	75 (60-80)	72 (49-82)
12	Rest	30 (10-40)	34 (9-58)
	Movement	60 (40-70)	50 (28-79)
24	Rest	22 (8-50)	36 (6-50)
	Movement	57 (22-70)	50 (36-68)

Data are expressed as median (interquartile range).

\*  $P = 0.01$ , significant difference.

Table 3. Adverse Effects

	Postoperative time (h)	Placebo group	Bupivacaine group
Sedation	0	1 (1-1)	1 (0-2)
	8	0 (0-1)	1 (0-2)
	12	1 (0-1)	0 (0-2)
	24	0 (0-0)	1 (0-2)*
Nausea	0	0 (0-0)	0 (0-0)
	8	0 (0-1)	0 (0-1)
	12	0 (0-0)	0 (0-1)
	24	0 (0-1)	0 (0-1)

Data are expressed as median (interquartile range).

\*  $P < 0.01$ , significant difference.

used a larger dose over the 24-hour study period, and it is possible that visceral nociceptive conduction was blocked after systemic absorption. This hypothesis is supported by the systemic action of lidocaine. In a clinical trial of 40 patients undergoing radical retropubic prostatectomy, IV lidocaine significantly decreased morphine consumption and total pain scores compared with placebo (9). From studies in rat models, it is thought that systemic lidocaine has peripheral and central actions. Peripherally, it suppressed ectopic impulse discharge (10), and centrally, it inhibited excitatory responses to iontophoretic glutamate (11).

No adverse effects were detected from the dose of bupivacaine and epinephrine used in our study. This observation is consistent with pharmacokinetic studies in which no adverse clinical effects were reported from intraperitoneal bupivacaine (12-14). In these studies, bupivacaine was administered in doses similar to that of our study, and peak plasma concentrations were much smaller than the generally accepted toxic value of  $3 \mu\text{g/mL}$  (15).

The benefit of reducing morphine consumption is thought to be related to improved recovery from surgery and anesthesia. In the postoperative period, analgesia, sedation, nausea, and return of bowel motility are important factors that facilitate recovery. Although there was a significant reduction in the visual analog scale on awakening in the Bupivacaine group compared with the Placebo group, other adverse effects

such as sedation and nausea were not reduced. However, there was little sedation or nausea in the 24-hour period, and our failure to demonstrate any significant difference may have been related to the fact that the categorical scoring system used was not sensitive enough.

We conclude that a combination of incisional and intraperitoneal bupivacaine with epinephrine may be recommended because it reduces pain on movement on awakening and provides significant supplemental morphine-sparing analgesia for four hours after TAH.

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INTRAPERITONEAL AND INCISIONAL BUPIVACAINE

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## Original Article

# Randomized controlled trial investigating the effect of transcervical papaverine and bupivacaine on postoperative analgesia following laparoscopic sterilization

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## Summary

**Background and objective:** A critical factor that delays patient discharge following day-surgery is severe postoperative pain and the requirement for strong analgesics. Laparoscopic sterilization is a day case procedure and is associated with additional postoperative pain compared with diagnostic laparoscopy. This pain, associated with application of Filshie clips, may be ischaemic or spasmodic in aetiology. Papaverine relaxes smooth muscle, and the aim of the study was to investigate if papaverine would be effective in improving postoperative pain if administered directly to the Fallopian tubes. Bupivacaine is used commonly in day-surgery and so we compared the effect of this local anaesthetic with saline placebo.

**Methods:** Sixty-six ASA I–II females undergoing laparoscopic sterilization were entered into the prospective, randomized, double-blind, placebo-controlled clinical trial. They received intrauterine papaverine (30 mg) or bupivacaine (0.375% 30 mL) or normal saline (30 mL) via the transcervical route before application of Filshie clips.

**Results:** There were no significant differences in the postoperative period between the three groups in the number of patients needing analgesia in the first 60 min postoperatively, the time to first analgesia, the rescue analgesic or antiemetic consumption, the incidence of postoperative nausea and vomiting, and the sedation and visual analogue pain scores.

**Conclusions:** From the data presented, we would not recommend routine transcervical administration of papaverine or bupivacaine for pain following laparoscopic sterilization.

**Keywords:** PAIN, postoperative; PHARMACOLOGY, papaverine; ANAESTHETICS, LOCAL, bupivacaine; SURGERY, laparoscopy; RANDOMIZED CONTROLLED TRIALS.

## Introduction

A critical factor that delays discharge and leads to hospital admission is pain after day case surgery [1]. Laparoscopic sterilization is a common procedure and

in comparison with diagnostic gynaecological laparoscopy, it is believed that tight clips or rings applied to Fallopian tubes cause additional pain [2] induced by ischaemia or spasm [3]. Therefore, drugs with local anaesthetic or muscle relaxant properties may be useful: the former in blocking neural conduction and the latter in reducing tubular spasm.

Papaverine is a smooth muscle relaxant that acts via phosphodiesterase inhibition [4]. It is instilled commonly into the male genital system for treatment of impotence. It has been used for cerebral vasospasm

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following subarachnoid haemorrhage, intermittent claudication and visceral spasm. The aim was to evaluate if transcervical papaverine would reduce abdominal pain after laparoscopic sterilization and to compare this effect with those of transcervical bupivacaine and normal saline.

## Methods

After obtaining local Institutional Ethics Committee approval, we studied 66 females of ASA Grades I–II undergoing laparoscopic sterilization. After signed informed consent had been obtained from the patients, they were allocated randomly to one of three treatment groups: bupivacaine, papaverine and placebo (Fig. 1). These groups were determined by computerized random number generation in blocks of six. Pain assessments and the provision of postoperative rescue analgesia were explained preoperatively.

Exclusion criteria included known allergies to bupivacaine and papaverine, diagnosed chronic pain syndrome, pelvic inflammatory disease, pelvic adhesions and a history of regular analgesic ingestion.

In addition, patients were excluded if they were unsuitable for a laryngeal mask airway or the use of diclofenac suppositories, and if they could not comply with the pain assessment used postoperatively. Exclusions concerning surgery were operative difficulties such as incorrect insufflation, conversion to an open procedure, use of more than one clip to one Fallopian tube and the application of the clip on the lateral two-thirds of the Fallopian tube.

All patients were given a standard general anaesthetic, comprising propofol  $2\text{--}4\text{ mg kg}^{-1}$ , fentanyl  $1\text{ }\mu\text{g kg}^{-1}$  and a muscle relaxant at induction of anaesthesia. Patients' lungs were ventilated to normocapnia with nitrous oxide and isoflurane in oxygen via a standard laryngeal mask airway. Suppositories of diclofenac 100 mg and intravenous (i.v.) ondansetron 4 mg were given to all patients at the beginning of surgery. Residual neuromuscular block was antagonized with neostigmine 2.5 mg with glycopyrrolate 500  $\mu\text{g}$ . In the postoperative period, rescue analgesia comprised oral codeine 60 mg with oral paracetamol 1 g, and intramuscular morphine 10 mg if necessary. An independent person prepared the

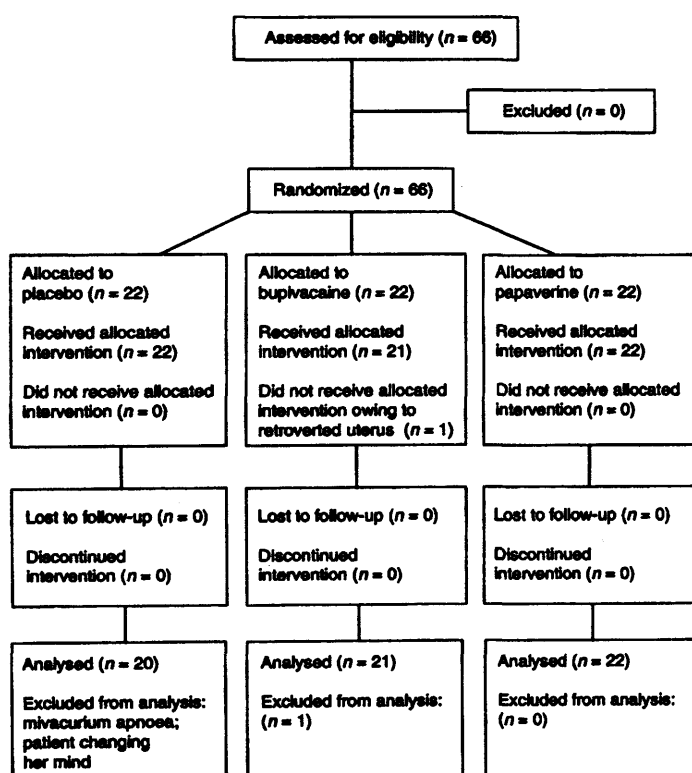


Figure 1. Enrolment, intervention allocation, follow-up and data analysis.

appropriate solution from instructions in the sealed randomized envelopes; these comprised saline 0.9% 30 mL, bupivacaine 0.375% 30 mL and papaverine 30 mg in saline 0.9% 30 mL.

Of the appropriate solution, 30 mL was carefully injected through a Spackman's cannula placed into the cervix of the uterus before the Filshie clips were applied. The syringe was left at the end of the cannula to prevent reverse flow of drug out of the cannula. A Filshie clip was applied to the medial one-third of each Fallopian tube. Manipulation of the uterus during sterilization was carried out using the Spackman's cannula. Records were made of the time of drug administration and any difficulties during the procedure.

In the postoperative period, visual analogue pain scores were recorded at rest on a scale of 0 (no pain) to 100 mm (worst imaginable pain). Assessments were made on awaking, 30 min later and then at 1, 2, 3 and 4 h after operation by an observer blinded to the patient group. Time to any rescue analgesia was recorded. In addition, side-effects such as hypotension, nausea and vomiting were recorded. At the same time intervals, suitability for discharge was assessed using our hospital's day-surgery unit guidelines.

From a previous study [5] on the efficacy of local anaesthetics administered to patients undergoing laparoscopic sterilization, it was estimated that 21 patients per group were needed for a 90% chance of detecting a 40% reduction in the proportion of patients requesting rescue analgesia within the first postoperative hour. Data were analysed by study of variance and Kruskal-Wallis tests for normally and non-normally distributed data respectively. Kaplan-Meier survival analysis analysed data of the time to first analgesia and a log rank test tested for statistical significance of the graphical data.

## Results

Of the 66 patients recruited into the trial, three did not complete the study. One patient in the saline group had prolonged apnoea to mivacurium requiring admission to the intensive care unit. On further investigation, she had plasma cholinesterase deficiency. Another patient in the same group changed her mind and declined to participate in the study. One patient in the bupivacaine group was excluded because of a retroverted uterus that did not allow transcervical administration.

The three groups were similar in physical characteristics. There were no significant differences in mean age and median body mass index (BMI) between the three groups.

There were no significant differences in the median visual analogue pain scores between the three groups

at all times in the postoperative period (Table 1). The time to first analgesia and median survival times did not differ significantly between the three groups (Fig. 2 and Table 2).

Analgesic consumption did not differ significantly between the three groups in terms of the number of patients in each group: who did not require analgesia; who had codeine 60 mg with paracetamol 1 g only; morphine only; or the combination of codeine 60 mg with paracetamol 1 g and morphine (Table 3). In addition, the number of patients in each group receiving analgesia within the first postoperative hour did not differ significantly.

Table 1. Visual analogue pain scores (mm).

Time (h)	Placebo	Bupivacaine	Papaverine	P
0	34 (19–68)	35 (29–47)	20 (15–45)	0.52
0.5	50 (35–79)	66 (51–70)	55 (19–75)	0.87
1	44 (22–69)	60 (56–70)	60 (15–79)	0.39
2	27 (13–52)	35 (30–45)	47 (4–72)	0.51
3	22 (11–45)	17 (5–35)	13 (4–51)	0.16
4	11 (1–24)	12 (2–24)	8 (0–23)	0.81

Data are median (interquartile range).

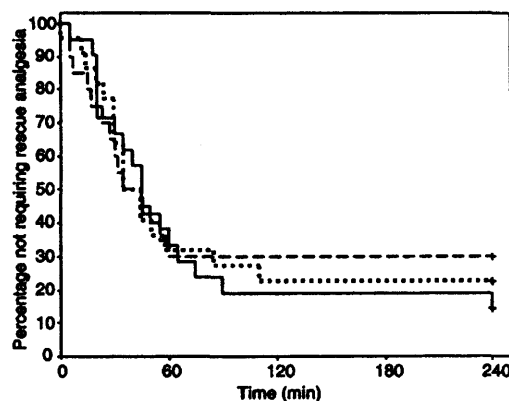


Figure 2. Time to first analgesia in the postoperative period (Kaplan-Meier survival analysis). ---: Placebo; .....: papaverine; —: bupivacaine.

Table 2. Time to first administration of analgesia (min).

0.9% Saline	Bupivacaine	Papaverine	P
35 (17–240)	45 (20–75)	35 (30–110)	0.93

Data are median (interquartile range).

Table 3. Analgesic consumption.

Analgesic	Placebo (n = 20)	Bupivacaine (n = 21)	Papaverine (n = 22)	P
None	6	3	5	0.49
Codeine 60 mg paracetamol 1 g	13	17	16	0.52
Morphine 10 mg only	7	3	6	0.30
Codeine 60 mg paracetamol 1 g morphine 10 mg	5	2	5	0.39
No. of patients requiring analgesia within the first hour postoperatively	13	13	15	0.912

Data are numbers of patients.

Table 4. Antiemetic consumption, postoperative nausea and vomiting.

Side-effects	Placebo (n = 20)	Bupivacaine (n = 21)	Papaverine (n = 22)	P
Nausea and vomiting after operation	5	2	5	0.37
Antiemetic given	3	2	3	0.87

Data are numbers of patients.

The combined incidence rate of postoperative nausea and vomiting was 19%. There was no significant difference between the groups in postoperative nausea and vomiting or requirement for additional antiemetics (Table 4). Sedation scores were low and did not differ significantly between groups. In addition, no adverse effects of bupivacaine or papaverine, e.g. hypotension, were detected.

## Discussion

It was found that neither intrauterine papaverine nor intrauterine bupivacaine improved analgesia with rectal diclofenac 100 mg following laparoscopic sterilization with Filshie clips. Papaverine is effective for treating conditions in which there is muscular spasm, and bupivacaine is effective in blocking neural conduction. It may be that our failure to demonstrate a significant analgesic effect arises in the method of administration. Although transcervical administration allows drugs to be targeted directly to the site of application of the clips, there may be substantial loss into the peritoneal cavity via the lateral ends of the Fallopian tubes, despite careful, slow administration. A more viscous preparation such as a gel with the same dose of drug may possibly be effective and this warrants further evaluation.

The dose of bupivacaine and papaverine should have been sufficient to produce analgesia. In a study similar to the present one, a slightly higher dose of bupivacaine 0.25% 50 mL was associated with a

reduction in the consumption of analgesic drugs postoperatively [6]. However, very high doses of bupivacaine would increase the risk of toxicity.

Clinical studies concerning the use of antispasmodic and local anaesthetic drugs in the treatment of pain after laparoscopic sterilization have demonstrated variable success. Previous prospective double-blind placebo-controlled randomized clinical trials have shown that pain may be reduced with glycopyrrolate 0.3 mg i.v. given before induction of anaesthesia [7] but not with i.v. buscopan [8,9]. Application of lidocaine gel 2% to Filshie clips was ineffective in one trial [10] but beneficial in another [5]. Lidocaine 1% given intermittently via a catheter placed intraoperatively into the Pouch of Douglas [11] or lidocaine 1% administered into the subserosal aspect of the cornual end of the Fallopian tubes [12] has been shown to reduce pain intensity after laparoscopic sterilization. Bupivacaine 0.5% applied topically to each Fallopian tube under direct vision relieves the intensity of pain after operation and increases the time to first analgesia [13]. In addition, intraoperative application of bupivacaine 0.5% to the mesosalpinx via a long suprapubic needle has produced similar benefits [14,15].

In conclusion, we found that papaverine 30 mg or bupivacaine 0.375% 30 mL administered into the uterine cavity and Fallopian tubes via the transcervical route did not provide additional analgesic effects following laparoscopic sterilization. Consequently, we do not recommend their routine administration.

### Acknowledgement

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## Does the opioid-sparing effect of rectal diclofenac following total abdominal hysterectomy benefit the patient?

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**Background.** The aim of this prospective, double-blind, randomized, placebo-controlled clinical trial was to investigate the opioid-sparing effects of rectal diclofenac following total abdominal hysterectomy.

**Methods.** Forty ASA I–II patients, aged 20–60 yr, were randomized to receive identical-looking suppositories of either diclofenac 75 mg or placebo, twice daily. All patients were given a standardized anaesthetic, with intravenous morphine via a patient-controlled analgesia device and either diclofenac or placebo for postoperative analgesia.

**Results.** The median 24 h morphine consumption (interquartile range) was significantly higher ( $P=0.02$ ) in the placebo group [59 (45–85) mg] than in the diclofenac group [31 (14–65) mg]. In comparison with the placebo group, there were significant reductions in total pain score in the diclofenac group at rest ( $P=0.04$ ) and on movement ( $P<0.01$ ). Total (SD) sedation score was significantly lower ( $P=0.04$ ) in the diclofenac group [90 (73) mm] than in the placebo group [148 (89) mm]. Total (interquartile range) nausea score was significantly lower ( $P<0.01$ ) in the diclofenac group [14 (0–53) mm] than in the placebo group [64 (30–109) mm]. There was no significant difference between the two groups of patients in episodes of vomiting or number of rescue antiemetics.

**Conclusions.** Rectal diclofenac reduces morphine consumption, improves postoperative analgesia, and reduces the incidence of adverse effects such as sedation and nausea.

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**Keywords:** analgesics anti-inflammatory, non-steroidal; analgesics non-opioid, diclofenac; analgesics opioid, morphine; vomiting, nausea

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Pain in the postoperative period is a critical factor that impedes recovery from surgery and anaesthesia. Despite the fact that total abdominal hysterectomy (TAH) is usually performed through a Pfannenstiel incision, patients still experience much abdominal pain during the first 24 h after surgery. At our institution, the current standard analgesic for this group of patients is intravenous morphine via a patient-controlled analgesia (PCA) device. The consumption of morphine is high, particularly in the initial postoperative period.<sup>1,2</sup> Morphine can cause adverse effects such as sedation, nausea and vomiting. Other methods of analgesia that have morphine-sparing effects are therefore required so that postoperative morbidity can be minimized.

Diclofenac is a non-steroidal anti-inflammatory analgesic that may reduce morphine consumption after TAH.<sup>3–4</sup> The aim of the study was to assess if decreased morphine

consumption is associated with a reduction in sedation and nausea and vomiting, in addition to improved analgesia. Elimination of these adverse effects is important to facilitate recovery from surgery.

### Methods and results

After obtaining local institutional Research Ethical Committee approval and informed patient consent, we studied 40 ASA I–II patients, aged 20–60 yr, scheduled for TAH. Patients were excluded if the hysterectomy was indicated for malignancy, or if there was a history of chronic pain, continuous usage of analgesic drugs, inability to tolerate diclofenac, or inability to use the PCA device.

All patients were given a standardized anaesthetic comprising propofol 2–4 ml kg<sup>-1</sup>, a non-depolarizing

## Opioid-sparing effects of diclofenac after total abdominal hysterectomy

neuromuscular blocking drug, morphine 10 mg i.v. and prochlorperazine 12.5 mg i.m. Their lungs were ventilated with nitrous oxide and isoflurane in oxygen, via a tracheal tube. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg with glycopyrrolate 500 µg.

Patients were allocated randomly to receive either diclofenac or placebo. Identical looking suppositories of diclofenac 75 mg and placebo were prepared by our pharmacy. Each patient was allocated to a numbered container holding four matching suppositories. The first suppository was given after induction of anaesthesia. Subsequently, suppositories of the same content were given on three occasions, at 12 hourly intervals.

In the postoperative period, assessments were made by a member of staff blinded to the treatment, on awakening of the patient and then at 8, 12 and 24 h. Sedation, nausea and pain at rest and on movement (deep inspiration) were assessed on linear analogue scales ranging from 0 mm for wide awake, no nausea, and no pain, to 100 mm for very drowsy, worst possible nausea, and worst pain imaginable. Patients who were too drowsy to assess themselves were scored as 100 mm for sedation and 0 mm for nausea by the observer. In addition, the number of instances of vomiting and the number of doses of rescue antiemetic were recorded. Morphine consumption was recorded by the PCA device.

We considered that in order to avoid the potential adverse effects of morphine, diclofenac should be able to reduce morphine consumption in the postoperative period by 50%; this reduction was considered clinically important because smaller reductions in morphine consumption have not been associated with improvements in the number of adverse effects.<sup>3</sup> From a previous study on non-steroidal anti-inflammatory drugs, it was estimated that to have an 80% chance of detecting a reduction in morphine consumption from 38 mg to 19 mg in the first 24 h after surgery, 16 patients per group would be required.<sup>5</sup>

Data were analysed in Excel 2000 and SPSS 9.5. To assess the cumulative adverse effects over the 24 h period, pain scores at rest and on movement, sedation scores, nausea scores, number of vomiting episodes, and number of antiemetic administrations were summed from the values taken on awakening, and at 8, 12 and 24 h. Data were assessed for normality using the Kolmogorov-Smirnov test. Data were analysed using the chi-squared test, *t*-test and Mann-Whitney test, as appropriate.  $P < 0.05$  was considered statistically significant.

Of 40 patients, six did not complete the study. In the diclofenac group, one patient had a midline incision and another patient withdrew herself from the study. In the placebo group, at least one suppository was omitted in two patients, one patient had insufficient pain relief, and haematemesis occurred in one patient.

There was no significant difference between the groups in weight and ASA status of the remaining patients. The median morphine consumption in the first 24 h and total

Table 1 Baseline characteristics and results. Age, weight, duration of surgery, total pain at rest and on movement, and sedation are expressed as mean (SD); 24 h morphine consumption, total nausea, total vomiting episodes, and total antiemetic administrations are expressed as median (interquartile range); ns, not significant

	Placebo (n=16)	Diclofenac (n=18)	P
Age (yr)	44 (00-00)	46 (00-00)	ns
Weight (kg)	74 (17)	71 (8)	ns
ASA III	8/8	12/6	ns
Duration of surgery (min)	65 (19)	75 (21)	ns
24 h morphine consumption (mg)	59 (45-85)	31 (14-65)	0.02
Total pain at rest (mm)	132 (55)	85 (72)	0.04
Total pain on movement (mm)	213 (76)	130 (94)	<0.01
Total sedation (mm)	148 (89)	90 (73)	0.04
Total nausea (mm)	64 (30-109)	14 (0-53)	<0.01
Total vomiting episodes	0 (0-0)	0 (0-1)	ns
Total antiemetic administrations	1 (0-2)	1 (0-1)	ns

pain scores at rest and on movement were significantly higher in the placebo group than in the diclofenac group. Although there were no significant differences between the groups in the number of vomiting episodes and number of doses of rescue antiemetics in the first 24 h after surgery, there were smaller scores for total sedation and total nausea in the diclofenac group (Table 1).

### Comment

We have found that rectal diclofenac was associated with significant 24 h morphine-sparing effects in comparison with placebo. In addition, total pain, sedation and nausea scores were significantly lower in the diclofenac group than in the placebo group. However, there was no significant difference between the two groups in vomiting or consumption of rescue antiemetic.

The morphine-sparing effects of diclofenac in our study concur with the findings of other studies.<sup>3,4</sup> However, although previous studies have demonstrated that diclofenac had morphine-sparing effects, this was not associated with a reduction in sedation and nausea.<sup>3,4,6</sup> This inability to detect a significant difference may have been related to the categorical scoring system used to measure sedation<sup>3,6</sup> and nausea;<sup>3,4</sup> in contrast, we assessed sedation and nausea using linear analogue scales.<sup>7,8</sup>

Our results concur well with another study in which ketorolac 30 mg i.v. reduced both morphine consumption and sedation on the first postoperative evening.<sup>9</sup> In this study, assessments were also made using a standardized linear analogue scale.

Tenoxicam is another non-specific cyclo-oxygenase inhibitor that is given intravenously. In a clinical trial involving 45 patients undergoing TAH, however, tenoxicam 20 mg or 40 mg i.v. was not found to produce a significant reduction in fentanyl consumption via PCA, pain scores or side-effects such as nausea.<sup>10</sup>

We conclude that diclofenac as prescribed in our study can be recommended, for it provides morphine-sparing analgesia and improves postoperative adverse effects such as sedation and nausea. These are important considerations in facilitating recovery from surgery and anaesthesia.

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## Analgesic effects of parecoxib following total abdominal hysterectomy<sup>†‡</sup>

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**Background.** Forty-eight ASA I–II patients undergoing total abdominal hysterectomy (TAH) were studied in a double blind, randomized placebo controlled trial of parecoxib for postoperative analgesia.

**Methods.** All patients were given propofol 2–4 mg kg<sup>-1</sup> i.v., a non-depolarizing muscle relaxant, morphine 10 mg i.v. and prochlorperazine 12.5 mg i.m. intraoperatively. Their lungs were ventilated with nitrous oxide and isoflurane 1–1.5% in oxygen. Morphine was self-administered for postoperative analgesia via a patient controlled analgesia (PCA) device. Patients were allocated randomly to receive either parecoxib 40 mg i.v. or normal saline on induction of anaesthesia.

**Results.** Twelve patients did not complete the study. Of the remaining 36 patients, there was no significant difference between the treatment groups in age, weight, ASA status, duration of surgery, or intraoperative dose of morphine. However, mean (95% CI) 24 h morphine consumption of 54 (42–65) mg in the parecoxib group was significantly ( $P=0.04$ ) lower than that of 72 (58–86) mg in the placebo group. Pain intensity scores on sitting up were significantly lower ( $P=0.02$ ) in the parecoxib group compared with placebo. There was no significant difference between the treatment groups in pain intensity scores at rest and on deep inspiration, or in nausea, total number of vomiting episodes, median number of rescue antiemetic doses, and sedation scores.

**Conclusions.** Parecoxib 40 mg i.v. may be recommended in patients having TAH as it provides morphine-sparing analgesia.

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Pain in the postoperative period is a critical factor that impedes recovery from surgery and anaesthesia.<sup>1</sup> Total abdominal hysterectomy (TAH) is usually performed through a Pfannenstiel incision and patients experience considerable abdominal pain requiring administration of strong opioids during the first 24–48 h after surgery.

At our institution, the current management of postoperative pain following TAH involves the use of morphine administered by a patient controlled analgesia (PCA) device. The dose of morphine is high, particularly in the initial postoperative period.<sup>2,3</sup> Administration of morphine is associated with adverse effects such as bowel immotility, and nausea and vomiting, in addition to sedation.<sup>1</sup> Thus,

other analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) are used to reduce the dose of morphine,<sup>4</sup> and hence minimize postoperative morbidity. Currently available NSAIDs such as diclofenac and ketorolac,<sup>5</sup> are non-selective inhibitors of both cyclo-oxygenase 1 (COX-1) and 2 (COX-2) enzymes. Parecoxib is the only currently

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available COX-2 selective inhibitor for i.v. administration and hence is suitable to use in the perioperative period.<sup>6</sup>

The primary aim of this study was to quantify the morphine-sparing effect of parecoxib. The secondary aim was to see if this analgesic effect leads to reductions in postoperative pain intensity, nausea, vomiting, consumption of rescue antiemetics, and sedation.

## Methods

After obtaining local research Ethics Committee approval and informed patient consent, we studied 48 ASA I–II patients undergoing TAH via a Pfannenstiel incision. Patients with diagnosed malignancy or with chronic pain were excluded.

All patients were given a standardized general anaesthetic comprising i.v. propofol 2–4 mg kg<sup>-1</sup>, a non-depolarizing muscle relaxant i.v., morphine 10 mg i.v. and prochlorperazine 12.5 mg i.m.. Their lungs were ventilated with nitrous oxide, and isoflurane 1–1.5% in oxygen. At the end of surgery, residual neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrrolate 500 µg. For postoperative analgesia, patients received morphine by PCA delivering morphine 1 mg i.v. with a lockout time of 5 min. For escape analgesia, patients were given a bolus of morphine 5 mg i.v..

Patients were allocated randomly to receive either parecoxib 40 mg i.v. in 2 ml, or 2 ml of normal saline on induction of anaesthesia. Both solutions were colourless and were prepared from instructions enclosed in an opaque envelope, by an anaesthetist who was not involved further in the study. Using computer-generated random numbers, randomization of treatment was performed in blocks of six, so that additional patients could be recruited as necessary.

Hourly morphine consumption was recorded from the PCA device. In addition, pain assessments were made on awakening, and then at 1, 4, 8, 12, and 24 h, by a member of staff blinded to the treatment. Abdominal pain intensity at rest, on deep inspiration, and on sitting up was assessed using the visual analogue scale (VAS). Patients marked a point on the 100 mm horizontal line representing their pain ranging from 'no pain' on the left to 'worst pain imaginable' on the right.

Nausea and sedation were also assessed on VAS ranging from 0 mm for no nausea and fully awake to 100 mm for worst possible nausea and very drowsy, respectively. Patients who were too drowsy to assess themselves were scored at 100 mm for sedation and 0 mm for nausea. In addition, the number of instances of vomiting and number of doses of rescue antiemetic were recorded.

Previous work<sup>7</sup> on patients having TAH has shown that mean 24 h morphine consumption would be expected to be 51 mg. From the data and a combined SD of 21 mg, we have estimated that to have an 80% chance of detecting a 35% or 18 mg reduction in 24 h morphine consumption in the parecoxib group compared with placebo, at a level of

$P < 0.05$ , a population of 42 patients would be required. Data were analysed using Excel 2000 and SPSS 9.5. Data were assessed for normality using the Kolmogorov–Smirnov test, and were analysed using the  $\chi^2$  test, Student's *t*-test, Mann–Whitney test, and analysis of variance for repeated measures.  $P < 0.05$  was considered statistically significant.

## Results

Of 48 patients, 12 did not complete the study for surgical and analgesic violations. Four patients had a midline incision after further examination under general anaesthesia, one patient had an abscess and so TAH was not performed, one patient had an abdominoplasty in addition to a TAH, and one patient had a subtotal abdominal hysterectomy. The PCA failed to work on the ward in one patient, the i.v. cannula tissue in another, and acetaminophen and meperidine were given to two and one patient, respectively.

Of the remaining 36 patients, there was no significant difference between the treatment groups in age, weight, ASA status, duration of anaesthesia (Table 1), and intraoperative dose of morphine (Table 2). However, mean (95% CI) 24 h morphine consumption of 54 (42–65) mg in the parecoxib group was significantly lower than that of 72 (58–86) mg in the placebo group ( $P = 0.04$ ) (Table 2). In addition, pain intensity scores on sitting up were significantly ( $P = 0.02$ ) lower in the parecoxib group than in the placebo group ( $P = 0.02$ ) (Table 3). There was no significant difference between the two groups in total number of vomiting episodes, number of rescue antiemetic doses (Table 2), pain intensity scores at rest and on deep inspiration, nausea, or sedation (Table 3).

## Discussion

In patients undergoing TAH, we found that parecoxib 40 mg i.v. was associated with significant reductions in 24 h morphine consumption and pain intensity on sitting up in comparison with placebo. However, there was no significant difference between the two groups in pain intensity at rest or on deep inspiration, nausea, number of vomiting episodes, rescue antiemetic consumption, or sedation. Of 48 patients studied, 12 had to be excluded for violations in protocol that were beyond our control. Despite this problem, we were able to show statistically significant results from 36 patients and thus it is unlikely that a type II error has occurred.

Our study is in agreement with another study of patients having TAH in which patients received two doses of parecoxib 40 mg i.v. in 24 h.<sup>7</sup> Tang found a reduction in mean 24 h morphine consumption of 36% in the parecoxib group compared with the placebo group.<sup>7</sup> This reduction was greater than that of 26% in our study, and is consistent with the lower dose (half maximum recommended daily dose) of parecoxib used in our study. However, in contrast to our study, there was no significant difference in pain scores between the two treatment groups in the study by

**Table 1** Baseline characteristics. Age, weight and duration of anaesthesia are expressed as mean (95% CI)

	Placebo	Parecoxib
Number of patients (included/excluded)	17/6	19/4
Age (yr)	43 (39–48)	43 (39–48)
Weight (kg)	72 (67–77)	69 (62–75)
ASA I/II	13/4	14/5
Duration of anaesthesia (min)	73 (59–88)	72 (59–84)

**Table 2** Morphine consumption, episodes of vomiting and rescue antiemetic consumption. Data expressed as mean (95% CI). Unpaired, two-tailed *t*-test for analysis of morphine consumption. Mann-Whitney test for total vomiting and antiemetic consumption. Statistical significance when *P* < 0.05

	Placebo	Parecoxib	<i>P</i>
Intraoperative dose of morphine (mg)	10 (10–11)	10 (10–10)	0.53
Postoperative dose of morphine over 24 h (mg)	72 (58–86)	54 (42–65)	0.04
Total number of vomiting episodes	0 (0–0)	0 (0–0)	0.59
Total number of rescue antiemetic doses	2 (1–2)	1 (0–2)	0.06

Tang.<sup>7</sup> It is unclear in the earlier study how pain was assessed, but it is likely that we were able to detect a difference in pain scores because our assessment of pain on sitting up was more sensitive than assessments made at rest or on deep inspiration.

Our results concur with another study of similar design, involving rectal diclofenac, a non-selective NSAID, administered to patients undergoing TAH.<sup>1</sup> At its maximum recommended daily dose of 75 mg twice daily, diclofenac produced a 52% reduction in 24 h morphine consumption compared with placebo. Pain scores at rest and on movement, and sedation and nausea were also significantly reduced in the diclofenac compared with the placebo group. It is likely that the reduction in adverse effects was attributable to the large decrease in morphine consumption in the diclofenac group compared with placebo. The larger diminution in morphine consumption of 52% in the diclofenac study compared with 26% in our study may be attributable to the use of parecoxib at half its maximum recommended daily dose compared with diclofenac given in maximum recommended dosage.

COX enzymes are important physiologically for the formation of prostaglandins (PG). COX-1 is expressed constitutively in normal tissues as part of normal cellular function, whereas COX-2 is upregulated during inflammation. Traditional non-selective NSAIDs are associated with adverse effects that are related, in part, to COX-1 inhibition; these include gastrointestinal ulceration, renal failure, and bleeding.<sup>8</sup> In the perioperative period, many patients are at risk of these problems owing to enforced starvation,

**Table 3** VAS (mm). Data expressed as mean (95% CI). ANOVA for repeated measures. Statistical significance when *P* < 0.05

	Placebo	Parecoxib	<i>P</i>
Pain intensity at rest	57 (40–73) 59 (47–72) 42 (26–58) 29 (17–41) 22 (13–31) 27 (13–41)	61 (48–73) 57 (43–71) 32 (21–43) 27 (13–40) 15 (8–23) 28 (16–41)	0.71
Pain intensity on inspiration	65 (50–80) 62 (50–75) 43 (26–59) 36 (24–49) 29 (21–37) 26 (18–35)	55 (36–74) 58 (42–73) 37 (24–50) 31 (17–46) 25 (15–35) 39 (24–55)	0.13
Pain intensity on sitting up	79 (66–91) 74 (52–96) 68 (52–85) 70 (56–84) 56 (43–68) 54 (37–70)	70 (51–90) 59 (40–78) 53 (39–68) 43 (31–56) 47 (30–64) 45 (27–62)	0.02
Nausea	16 (0–31) 14 (1–27) 24 (4–44) 19 (1–38) 15 (3–26) 17 (2–33)	19 (1–38) 21 (5–37) 16 (2–31) 9 (3–14) 8 (0–17) 14 (0–29)	0.75
Sedation	65 (52–77) 72 (56–87) 53 (36–70) 57 (42–73) 41 (22–60) 55 (40–69)	68 (55–81) 78 (67–88) 71 (58–83) 57 (39–75) 59 (34–84) 35 (17–52)	0.16

dehydration, and tissue trauma. Whilst adverse effects are uncommon with non-selective COX inhibitors in healthy patients, their use in patients with peptic ulcer disease and renal impairment is contraindicated. A possible alternative in patients at risk of these problems is administration of COX-2 inhibitors.

The use of selective COX-2 inhibitors in comparison with non-selective NSAIDs has been investigated extensively in patients with arthritis. Two important randomized controlled trials, the CLASS<sup>9</sup> and the VIGOR,<sup>10</sup> have shown a significant reduction in upper gastrointestinal complications with celecoxib or rofecoxib compared with non-selective NSAIDs. This has been confirmed in a systematic review which showed that the relative risk (95% CI) of any upper gastrointestinal event with celecoxib compared with a non-selective NSAID was 0.54 (0.42–0.71) in patients treated for osteoarthritis or rheumatoid arthritis.<sup>11</sup> In a recent placebo case controlled population based study, the adjusted risk ratios (95% CI) of gastrointestinal haemorrhage for non-selective NSAIDs, a combination of diclofenac and misoprostol, rofecoxib, and celecoxib were 4.0 (2.3–6.9), 4.6 (2.5–8.2), 3.5 (2.4–5.0), and 1.7 (1.1–2.6), respectively.<sup>12</sup>

In the VIGOR study, it was found that the rates of cardiovascular events and in particular myocardial infarction were significantly higher in patients having rofecoxib than in those having naproxen.<sup>10</sup> The relative

risk of myocardial infarction (95% CI) was 0.2 (0.1–0.7) in the naproxen group, suggesting a coronary protective effect presumably from sustained platelet inhibition. In an attempt to disprove the possibility of a higher cardiovascular event rate in patients taking rofecoxib, there has been an assessment of cardiovascular thrombotic events in 23 phase IIb to V rofecoxib studies.<sup>13</sup> It was shown that the relative risk of an event between rofecoxib and placebo, between rofecoxib and non-naproxen NSAIDs, and between rofecoxib and naproxen was 0.84 (0.51–1.38), 0.79 (0.40–1.55), and 1.69 (1.07–2.69), respectively. Thus, it is possible to conclude that naproxen has no significant cardiovascular protective effect compared with rofecoxib. Also, it appears that rofecoxib may increase the risk of a cardiovascular event compared with naproxen. In a recent retrospective study, there was some evidence that any risk of a cardiovascular event with rofecoxib may be dose related.<sup>14</sup> In comparison with non-users and celecoxib users, respectively, the relative risk (95% CI) of a serious cardiovascular event was 1.93 (1.09–3.43) and 2.20 (1.17–4.10) in patients taking rofecoxib in doses exceeding 25 mg. There was no increased risk of these events in patients receiving lower doses of rofecoxib, or in those receiving doses of celecoxib >300 mg, naproxen ≥1000 mg or ibuprofen ≥1800 mg.

The evidence for any sparing of renal function from selective COX-2 inhibitors compared with non-selective NSAIDs is sparse. The CLASS study did show that the incidence of increased serum creatinine concentration and hypertension was significantly lower in patients receiving celecoxib compared with those taking NSAIDs.<sup>9</sup> However, these benefits were not detected in another RCT.<sup>15</sup>

The efficacy of celecoxib has been noted to be comparable with that of existing non-selective NSAIDs in a systematic review of patients with arthritic pain.<sup>11</sup> For postoperative pain management, there is evidence that celecoxib and rofecoxib are effective after spinal fusion,<sup>16</sup> and dental surgery.<sup>17</sup> However, the disadvantage of celecoxib and rofecoxib in anaesthetic practice is that they are given orally, when patients may have PONV and delayed gastric emptying. Parecoxib may be administered intravenously or intramuscularly, and hence is more useful in this respect.

Despite the possible theoretical benefits of selective COX-2 inhibitors compared with non-selective NSAIDs, their role in postoperative pain management remains to be determined. They may be useful in patients at risk of gastroduodenal ulceration, or after procedures such as tonsillectomy when postoperative haemorrhage is an uncommon but significant problem. However, it seems unlikely that currently available selective COX-2 inhibitors will find a role in patients with renal dysfunction.

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