Local analgesia for caesarean section pain relief: a randomised clinical trial, pharmacokinetic study and systematic review

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DECLARATION

I, Anthony Akinloye Bamigboye, declare that this thesis is my own work. It is being submitted for the award of the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg South Africa.

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PUBLICATIONS AND AWARDS

1. Bamigboye AA. Ropivacaine serum concentration following peritoneal spraying and wound infiltration for pain after caesarean delivery. *International Journal of Gynecology Obstetrics* 2009; 105(1):68-9.

2. Bamigboye AA, Hofmeyr GJ. Local anaesthetic wound infiltration and abdominal nerves block during Caesarean section for post-operative pain relief. *Cochrane Database of Systematic Reviews* 2009, Issue 3, CD006954. DOI: 10.1002/14651858.

3. Bamigboye AA, Hofmeyr GJ. Ropivacaine abdominal wound infiltration and peritoneal spraying at Caesarean delivery for pre-emptive analgesia. *International Journal of Gynecology and Obstetrics* 2008; 102(2):160-4.

4. Bamigboye AA, Hofmeyr GJ. Caesarean section wound infiltration with local anaesthesia for post-operative pain relief - any benefit? *South African Medical Journal* 2010; 100(5):313-9.

AWARDS

1. The John Schiarra Award for the best published research from a developing country (2008), as assessed by the International Federation of Gynecology and Obstetrics (FIGO) and the International Journal of Gynecology and Obstetrics (*see Publication 3. above*).
2. Faculty 1000 peer review award for 'scientific merit and the positive contribution it makes to the medical literature'. (*See Publication 2. above and Appendix 3.*).

LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ASICs	Acid sensing ion channels
ASA	American Society of Anesthesiologists
B adrenergic	Beta-adrenergic
Ca	Calcium
Cox	Cyclo-oxygenase
Cmax	Maximum serum concentration
CNS	Central nervous system
CI	Confidence interval
CS	Caesarean section
CV	Cardiovascular
FIGO	International Federation of Gynecology and Obstetrics
GA	General anaesthesia
HIV	Human immunodeficiency virus
IV	Intravenous
K	Potassium
LA	Local anaesthesia
LMWH	Low molecular weight heparin
L1	First Lumbar nerve root
MD	Mean difference

Na	Sodium
NMDA	N-Methyl D- aspartate
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RR	Relative risk
SMD	Standardised mean difference
SD	Standard deviation
VAS	Visual analogue score

EXECUTIVE SUMMARY OF THE THESIS

Caesarean section is the most widely performed major obstetric procedure. Even though regional block is often the anaesthesia of choice, general anaesthesia has its indications. Patients who deliver their babies by caesarean section under general anaesthesia deserve optimal pain management. Post-operative pain management is essentially multimodal, combining narcotics with non-steroidal anti-inflammatory and other interventions, including local anaesthetic infiltration in the wound or abdominal nerve blocks.

Alleviating post-operative pain by the use of adjuvant local analgesia has been researched for several decades with conflicting reports. However, many obstetricians routinely infiltrate the wound with local anaesthetics, despite a lack of consensus on the technique or route of administration. To my knowledge, no reviews or metaanalysis of data have been done to support this practice.

Most trials of local anaesthetics as an adjunct to pain relief have been carried out by using skin and subcutaneous wound infiltration. This technique of administration might have been responsible for producing conflicting results. Introducing a technique of anaesthetising all the layers of the anterior abdominal wound down to the peritoneum and comparing it to a placebo, may be one of a series of studies that can be undertaken to address the question of the efficacy of using local anaesthetics for post-caesarean section pain relief.

The first part of this thesis is an experimental study design of a randomised clinical trial that was published in the official journal of the International Federation of Gynecology and Obstetrics (FIGO), the International journal of Obstetrics and Gynecology, in August 2008. This double-blind, placebo-controlled trial investigated the efficacy of routinely infiltrating the caesarean section wound and needle spraying, or infiltrating, the peritoneum with the local

anaesthetic agent, ropivacaine. The objective of the trial was to assess the effect of this intervention on post-operative pain and the need for opioid use in the immediate post caesarean section period in women with planned surgical deliveries. The technique of infiltrating all layers of the abdominal wound was an innovation as compared to the subcutaneous and skin infiltration that has traditionally been carried out. The inclusion of the breached peritoneal surfaces was to address the deep pain of peritoneal injury that might occur from abdominal surgery. The results of this trial, using ropivacaine wound infiltration into all layers of the anterior abdominal wall, as adjuvant post-operative analgesia in elective caesarean sections for single uncomplicated pregnancies at term, showed a reduction in the need for narcotic analgesics and a reduction in the occurrence of severe post-operative pain in women undergoing general anaesthesia.

There appears to be no recommended dose of local anaesthetics for a caesarean section wound infiltration and peritoneal application therefore, for the trial, we were concerned about exceeding the safety limits. The risk of serum toxicity from peritoneal application of the local anaesthetic might be high as the absorption of drugs and fluids through the peritoneum is generally optimal. Hence, for the clinical trial, we adopted the dose used for brachial plexus block. If this baseline dose produced a serum concentration that was within the safety margin (less than toxic concentration); a dose finding trial of lesser concentration could be embarked upon. This motivated the need for the serum concentration study published in the International journal of Obstetrics and Gynaecology in January 2009. Using high performance liquid chromatography in 71 serum samples at different time intervals, the maximum concentration of ropivacaine using a dosage of 225mg by infiltration through all layers of the anterior abdominal wall incision, including the peritoneum at caesarean section was 1553 (SD 793) ug/L. This falls within the safety range in humans, and below levels reached following brachial plexus block.

The last part of the thesis combines all suitable randomised trials, including the clinical trial described above, in a systematic review, to advise health care providers on the role of adjuvant local anaesthetic infiltration in caesarean section pain relief. The decision to include the author's trial was made by an independent Cochrane reviewer based on strictly objective criteria.

The systematic review of the effects of this health care intervention of local anaesthetic infiltration in caesarean section wounds was edited by the Pregnancy and Childbirth group of the Cochrane collaboration, Liverpool, United Kingdom. The review addresses a clearly defined question and explains how studies for the review were located, selected and excluded. It gives details of the search strategy used, explains how data were collected from studies, how missing data were handled and how study quality was assessed. In twenty trials involving 1150 patients, it concludes that local anaesthetic wound infiltration and abdominal nerve blocks as adjuncts to regional and general anaesthesia, were of benefit in caesarean section by reducing opioid consumption. Non-steroidal anti-inflammatory drugs as an adjuvant conferred additional pain relief.

The importance and relevance of the systematic review, which was published in two peer review journals, can be inferred by the interest which it has generated in the press worldwide. This may provide indirect evidence of its potential to change clinical practice. A PhD thesis, inter alia, needs to contribute to the advancement of knowledge. The potential of the systematic review to achieve this was recognised by Faculty 1000, 'a revolutionary literature awareness service that identifies and evaluates the most important articles published in Medicine based on the recommendations of a Faculty of over 2000 peer-nominated leading researchers and clinicians', by way of an award.

Pain management, in the modern medical practice, is a sub-specialty that falls within the domain of anaesthetists. A thesis on the subject might appear not to be a primary responsibility of an obstetrician. However, after the anaesthetist has completed the broader duty of advising on post caesarean section pain management, it is the obstetrician who is faced with further augmenting or modifying pain relief prescribed by the anaesthetists. In addition, if wound infiltration is to be employed, the obstetrician who performs the procedure is better placed to administer the intervention intra-operatively. Based on this premise, it is appropriate that an obstetrician conducted studies on local anaesthetic as an adjunct to caesarean section pain relief.

CHAPTER ONE

REVIEW OF THE LITERATURE

Synopsis

The discovery, extraction and clinical applications of local anaesthetics in Europe, in the 19th century, brought about a quest for wider clinical applications in the decades that followed. Local anaesthetics wound infiltration appeared to be reasonable but in clinical studies, results were variable. In this chapter, I summarise the anatomy of the anterior abdominal wall, where the local anaesthetics will be applied. In addition, I discuss the pathophysiology of pain and pharmacology of local anaesthetics, and review the different modalities of management of post-caesarean section pain. Regional anaesthesia is the anaesthesia of choice for performing caesarean section but indications for general anaesthesia remain; these indications are discussed. The method of local anaesthetics assays using chromatography is discussed.

Child birth is a profoundly emotional experience for the mother and her family. This is a time when a new individual is added to the family, a time that is filled with age old rituals and modern routines. Ideally, this period should be as pain-free as possible to enable the mother to perform her immediate maternal and social responsibilities. Caesarean section delivery may predispose to negative emotions, especially if social support [1] and immediate post-operative pain management are sub-optimal.

Caesarean section is widely performed, and different rates for this procedure are quoted all over the world. What is certain is that the rates are ever increasing. The World Health Organisation recommends an optimum rate of 5-15% to ensure the best outcome for mother and neonate.[2] In the United Kingdom, in 2001, 21% of all deliveries was by caesarean section.[3] In the private health sector in South Africa, a much higher figure of 57% was noted in

a study published in 2002 [4] and 60.4% in another study published in 2009.[5] A major South African medical aid company reported a rate of 63% in a 2004 audit [6] and a study comparing the number of caesarean sections in South African government-funded institutions to private hospitals, found a 50% increase in the latter. [7]

Whilst regional anaesthesia (spinal and/or epidural block) is usually performed for caesarean section because it is safer and results in less morbidity, general anaesthesia is sometimes indicated. Approximately 16% of caesarean sections in the UK are performed under general anaesthesia and failure of regional anaesthesia accounts for 10% of these cases.[8] General anaesthesia is indicated if the patient declines a regional approach, if there is any clinical contraindication to neuraxial blockade e.g. coagulopathy, or when time is of immense necessity e.g. acute severe fatal compromise.[8] Lack of resources, manpower, skill and to a lesser extent, materials to insert a regional anaesthetic, are further reasons why general anaesthesia may be administered. Low resource centres may perform more caesarean sections under general anaesthesia: a report from a sub-Saharan University Teaching Hospital showed that all caesarean sections (8.4% of all deliveries in the centre) between January 2006 and April 2007 were performed under general anaesthesia.[9]

The management of post-operative pain for caesarean sections performed under general anaesthesia usually involves the use of opioids and non-steroidal anti-inflammatory drugs (NSAIDS). Such pain relief is often inadequate, especially within the first few hours following surgery.

Several studies on local anaesthetics for post-operative pain in general surgery have produced varying reports, ranging from being beneficial, [10, 11] to no benefit [12, 13]. Despite these conflicting reports, without the evidence and guidance from systematic reviews, the practice of local anaesthetic wound infiltration has slowly crept into the surgical routines of obstetricians. It is imperative to test medical practices by well conducted trials, where possible

and where there are doubts, before accepting such practices as the norm. [14] It is for this reason that I was motivated to understand and explore the use of local anaesthesia as an adjunct to post caesarean section pain relief.

1.1. The surgical anatomy of the anterior abdominal wall

Knowledge of the anterior abdominal wall anatomy is important to obstetricians and surgeons in general, before entering the abdominal cavity. This is important in discerning the locations of major blood vessels, nerves and the visceral organs, thereby avoiding injuries to tissues. For the anaesthetists and surgeons who perform abdominal nerve blocks, a sound knowledge of the anterior abdominal wall anatomy enables identification of the sites to be used and circumvents damage to the nerves and inadvertent intravascular injection of anaesthetic drugs.

1.1.1. The muscles and aponeurosis of the anterior abdominal wall

The hexagonal appearance of the outline of the anterior abdominal wall has boundaries of which the superior margin is termed the costal margin. The lateral boundary is the imaginary mid-axillary lines between the lateral part of the costal margin and the iliac crest. The inferior border on either side runs from the iliac crest, inguinal ligament, pubic crest and pubic symphysis. During laparotomy, the layers of the anterior abdominal wall, which are encountered from the skin inwards into the peritoneum, include the superficial fascia of Camper's and Scarpa's, a musculo-aponeurotic layer, transversalis fascia, a pre-peritoneal adipose layer and the parietal peritoneum.[15]

The absence of deep tendons in the muscles of the anterior abdominal wall facilitates ease of abdominal wall distension, for example, during breathing movements and in pregnancy. The functions of abdominal muscles

include flexing the trunk, as accessory muscles of respiration, defecation and protection of intra-abdominal organs against trauma. [16]

To aid mobility and distension of the abdominal wall, the skin over the anterior abdomen is more mobile than the skin covering the back. Skin creases run fairly horizontally above the umbilicus and infero-medially below and more distinct suprapubically. Transverse incisions made along the skin crease tend to heal better compared to incisions that are made perpendicular to the creases. Beneath the skin is a fascia of adipose tissue followed by the fibro-elastic layer (Scarpa's fascia). Beneath this fascia is a musculo-aponeurotic layer which is formed by the rectus abdominis muscles that come from either sides of the abdomen meeting at the midline. This layer is contained within the rectus sheath that is formed by division in the aponeurosis of the internal oblique muscle. Posteriorly, it is reinforced by the aponeurosis of the transversus abdominis and anteriorly by that of the external oblique. Anteriorly, the sheath is adherent to the rectus muscle whilst posteriorly, it is loose. The lateral muscles fill the space between the rectus and the lumbar muscles and between the costal margin and the iliac crest. The external oblique muscle arises by fleshy digitations from the outer aspect of each of the lower eight ribs near their costochondral junctions. The fibres of the external oblique pass downwards and medially, those of internal oblique run upwards and medially and those of transverses abdominis run transversely. Below this line, the muscles become aponeurotic and their fibres pass downwards and medially in the formation of the inguinal canal. The inguinal ligament is the rolled lower border of the aponeurosis of the external oblique.[16] The linea alba, which runs from the xiphoid process above to the pubic symphysis below, is a midline inter-digitation of the aponeurosis of the external oblique, internal oblique and transversus abdominis of one side with the other side. It is more pronounced and wider above the umbilicus than below. [15]

1.1.2. The lymphatic drainage

The lymphatic drainage of the lower abdominal wall consists of between 10 and 20 superficial interconnecting inguinal lymph nodes. These are located in the region of the inguinal ligament. Anastomoses are found between the lymph vessels of the right and left sides of the abdomen.[17]

1.1.3. Blood supply to the anterior abdominal wall and the peritoneum

The anterior abdominal wall has a rich blood supply. The posterior rectus sheath contains the inferior epigastric vessels which anastomose with the superior epigastric artery and vein, the terminal branches of the internal thoracic vessels. These vessels may be damaged during a rectus block, insertion of lateral trocar when performing a laparoscopy, or when inserting an intra-abdominal drain.[16] They may also be damaged when performing a transverse lower abdominal wall incision for caesarean section. The visceral peritoneum is supplied by the vessels from adjacent organs while the parietal peritoneum is supplied by branches from musculo-phrenic arteries, lumbar arteries, inferior epigastric and deep circumflex iliac vessels.

1.1.4. Nerve supply of the anterior abdominal wall and the peritoneum

The subcostal nerves (anterior primary rami of T7 to L10) lie between the internal oblique and transversus abdominis and supply the anterior abdominal wall. Each subcoastal nerve has a lateral cutaneous branch that goes through the rectus and innervates the overlying dermatome. The eleventh intercostal and subcostal nerve supply the dermatome below the umbilicus; the tenth supply the skin around the umbilicus while the seventh supplies the skin around the epigastrium (Figure 1.1). The iliohypogastric and ilioinguinal nerves (L1) supply the skin immediately above the inguinal ligament and pubic symphysis.[15, 16]These two nerves are relevant in transverse lower abdominal incisions and midline sub-umbilical incisions usually used for performing caesarean

sections. It is relevant to both wound infiltration analgesia and direct blockage of the ilioinguinal and iliohypogastric nerves.

The peritoneum is a layer of mesothelium which envelopes the abdominal and pelvic organs. It consists of the pain sensitive parietal peritoneum and stretch sensitive visceral peritoneum. The visceral peritoneum in the lower pelvis is supplied by the sympathetic nerves of underlying visceral. Apart from sensitivity to stretch, the receptors are also sensitive to ischemia and spasm of smooth muscles. The parietal peritoneum overlying the diaphragm is supplied by the innervations from C3-C5 hence referred pain to the shoulder dermatomes when irritated. The supply over the parietal peritoneum generally is from the lower thoracic to the first lumbar nerve roots. [18]

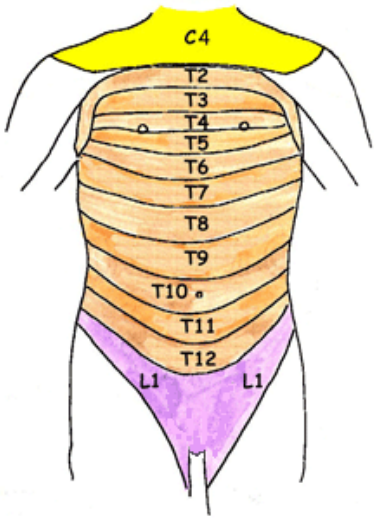

Fig 1.1. Dermatomes of the anterior abdominal wall [19]

The technique of ilioinguinal or iliohypogastric and the twelfth thoracic (T12) nerve block requires knowledge of its surface anatomy. The land mark for these nerves in surface marking is about 3cm inferior and 3cm medial to the anterior superior iliac spine. T12 and iliohypogastric nerves run between the internal oblique and the external

oblique muscles. The ilioinguinal nerves initially run between the transversus abdominis and the internal oblique muscles. Inferiorly thereafter, it pierces the internal oblique muscles around the region medial to the anterior superior iliac spine. It runs antero-medially to supply the muscles and skin in the inguinal and the suprapubic regions.[20] These are the areas of incision involved in performing a Pfannenstiel or modified Pfannenstiel caesarean section.

The technique of ilioinguinal and iliohypogastric nerve blocks

Several studies involving anterior abdominal nerve blocks as an adjunct to post caesarean section pain relief have been done. [21] The technique of ilioinguinal and iliohypogastric nerve blocks involves identification of the anterior superior iliac spine. Approximately one finger breadth below and lateral will identify the point of insertion of a 3.5 cm long, 22 gauge needle placed perpendicular to the skin. On piercing the external oblique muscle, a "click" may be felt where the first volume of local anaesthetic is injected to block the iliohypogastric nerve. A further, slightly deeper, advancement of the needle in the same plane gives the second "click feeling", that indicates the piercing of the internal oblique to block the ilioinguinal nerve. With the needle in situ, and redirecting it medially and laterally, volumes of local anaesthesia are infiltrated around the lateral cutaneous branches of the subcostal nerves. The use of an ultrasound guide to identify the nerves, improves the efficacy of local anaesthesia, compared to the use of anatomical land marks. Where resources are available, training with sono-anatomy prevents inadvertent nerve and visceral injuries. [20]

1.2. The history of caesarean section

Caesareans have been part of human medical history, both in the cultures of the western and the non-western worlds. This surgical procedure, over the centuries, has been the source myths, legends and heroes, in written and oral history. A study on post-caesarean section pain management would not be complete without a brief on how the procedure evolved into the modern procedure of the 21st century.

Deliveries by caesarean section, in the early ages, were essentially heroic and were performed to save the babies that would have otherwise perished with the mothers. The term 'caesarean section' was derived from the Latin word 'caedo' (to cut). It is unsure when the procedure was first performed. Legend has it that the Roman emperor, Julius Caesar, was born by a caesarean section but this was refuted in many quarters, because it was noted in history that Julius Caeser's mother lived to witness the golden reign of her son. It would have been an impossible feat to survive the complications of such surgery at that point in human medical history.

An emperor of Bindusara, India, is said to have been born by caesarean section during 320 BC, as was an Iranian icon, Rostam, in a book written in 1000 AD. In 1204, Saint Raymund Nonnatus was born by caesarean section ('nonnatus' means not born) as was King Robert II of Scotland in 1316, however neither of their mothers survived.[22, 23]

An animal husbandry practitioner, Jacob Nufer from Switzerland, was the first person recorded to perform a caesarean section during which the mother survived. In the United States, the first recorded caesarean section was in 1794. In Africa, caesarean section was first recorded in Uganda in 1879, performed by local African traditional healers, although in other regions it might have been performed much earlier. [22, 23]

Although survival was possible, it was not the norm, and the mortality rate in the United Kingdom for caesarean section in 1865 was 85%. In Paris, France, between the periods 1787 to 1876, there was no record of any maternal survivors. With improvement in medical practice, surgical techniques and the advent of anaesthesia in the nineteenth century, the mortality rate started declining. In 1882, Max Sanger introduced sutures in the form of silver wires to close the uterine incision. Marion Sims had earlier invented the wires to close vesico-vaginal fistulas.

With improved survival in the late nineteenth century, surgical attention was focused on the technique of performing caesarean sections to further reduce morbidity and mortality by preventing uterine rupture, reduce blood loss and sepsis. This was the reason for advocating lower segment caesarean section between 1880 and 1925 – a technique started by a Briton, Munro Kerr, and which was quickly taken up by the Americans. A further major reduction in mortality occurred after the discovery of penicillin by Alexander Fleming in 1928. With increasing safety of caesarean sections, came an increase in the rate of performing the procedure. Many more hospitals were built, medical knowledge improved and surgery became safer. This led to a further increase in caesarean sections, such that the high rates seen today are a source of concern in modern obstetrics. [22, 23]

1.3. Surgical incisions for performing caesarean section

The abdominal cavity may be explored surgically by vertical, transverse or oblique abdominal incisions. Traditionally, midline incisions were used for performing caesarean sections and, as in other surgical conditions, required a laparotomy. These later evolved to transverse lower abdominal incisions like the Pfannenstiel incision. Other transverse incisions used in the surgery of the anterior abdominal wall are the Joel-Cohen (a modified Pfannenstiel incision), Maylard transverse muscle cutting incision and the Kocher's subcostal incision. [24]

1.3.1. The midline incision

The midline incision has several advantages over other types of abdominal incisions including minimal injury to blood vessels, nerves and muscles, quick and wider access to the abdominal cavity [24] and the possibility of extension to the supra-umbilical midline of the epigastrium. [25] However, midline incisions do not give good cosmetic results and have a higher predisposition to wound breakdown and incisional hernias. Performing a caesarean section under local anaesthesia is more effective with vertical incisions. [26] A modification of the midline incision is the paramedian incision which may be easily extended above the umbilicus for improved intra abdominal exposure. The scar is not appealing but it is stronger, with less chance of herniation. [27]

1.3.2. The Pfannenstiel incision

The Pfannenstiel incision which was described in the beginning of the 20th century by Pfannenstiel, and with its various modifications over the decades, is used frequently by gynaecologists for access to the pelvic organs and for caesarean section.[28] The skin incision, which is made in a skin crease about five centimetres (cm) above the symphysis pubis, is approximately 12 cm long. The incision is carried deeper into the abdominal wall through fat and fascia until the rectus sheath is reached. The latter is then divided across the length of the incision exposing the anterior rectus muscle. The aponeurosis is separated towards the umbilicus superiorly and almost towards the pubis inferiorly. The rectus muscles are thereafter separated laterally to expose the underlying parietal peritoneum which is opened vertically and retracted to expose the lower segment of the uterus. Pfannenstiel incisions heal quite well with good apposition and cosmetics. [29]

1.3.3. Maylard, Cherney and Mouchel incisions

The Maylard incision is a slight modification of the Pfannenstiel incision where better exposure is necessary to deliver the baby. The rectus abdominis muscle is sharply dissected or cut. There is, however, more blood loss and more damage to muscular tissues. [29] Cherney's incision is also a muscle cutting incision like Maylard, but it involves dissecting the rectus attachment to the pubic symphysis. [30] A Maylard–type incision by Mouchel was described in 1981. The skin incision is at the line of pubic hair, which is therefore lower than the standard Maylard incision; it involves cutting the muscles above the opening of the inguinal rings.[31]

1.3.4. The Pelosi incision

A transverse suprapubic incision is cut and the subcutaneous and fat layer, deepened to the rectus fascia with electrocautery. The latter is sharply incised and the rectus muscle bluntly separated. The peritoneum is often entered bluntly, and the abdominal wound stretched to expose the uterus. The bladder is not reflected from the uterus and the baby is delivered. The placenta is allowed to separate spontaneously, and the uterus is closed in one layer. The advantage of a Pelosi's incision is the speed of surgery and reduced blood loss. [32]

1.3.5. The Joel-Cohen based incisions and techniques

These methods of performing a caesarean section are modifications to the Pfannenstiel incision technique. The skin incision is made about 3cm above a line joining the anterior superior iliac spines. The fat and the subcutaneous tissues are slightly opened at the centre - mostly with blunt dissection. The rectus is reached,

which is slightly opened sharply at the centre. The fingers are used to push the incision edges laterally for exposure. The peritoneum is entered often with blunt pushing and stretching and the uterus exposed. The uterus is closed in one layer. With non closure of the peritoneum, and avoidance of sharp dissection in most of the steps described above, the technique was popularised in the Misgav-Ladach Hospital in Israel. This method was named after the institution. The operating time was short, blood loss minimal, and with less post-operative pain. [33].

A Cochrane review [32] compared the Joel Cohen type of caesarean section to the traditional Pfannenstiel caesarean section and found reduced blood loss and reduced operating time in the former. In addition, there was reduced time to delivery of baby, less post-operative pyrexia, fewer analgesic consumption and shortened period of post-operative pain. The conclusion of this review was that the Joel Cohen based caesarean section was advantageous in reducing postoperative morbidity and reducing the cost associated with performing caesarean delivery. [32, 33]

Table 1.1, adapted from the WHO Reproductive Health Library, [29] describes the various techniques of performing caesarean section. After delivery of the baby, various approaches and methods of closure of the abdominal wound incision are described. This is summarised in the WHO Reproductive Health Library as depicted in Table 1.2.

Table 1.1. Types of incision of tissues in different techniques of caesarean section (Adapted from the Reproductive health Library). [29]

Technique	Skin	Subcutaneous layer	Rectus sheath	Rectus muscle	Peritoneum	Uterus
Pfannenstiel	Transverse Sharp	Not specified	Transverse Sharp dissection from muscles	Not specified	Longitudinal sharp	Transverse Lower segment
Pelosi-type	Transverse Sharp	Electrocautery Transverse	Electrocautery Transverse	Blunt separation	Blunt	Transverse Lower segment Blunt or sharp
Joel-Cohen	Transverse Sharp Higher than Pfannenstiel	Incision in midline, then blunt along with rectus sheath	Incision in midline, then blunt along with subcutaneous layer	Blunt separation	Blunt	Transverse Lower segment Blunt
Misgav-Ladach	Transverse Sharp Higher than Pfannenstiel	Not specified	Blind thrusting movement of the open scissor-tips	Not specified	Blunt	Transverse Lower segment Blunt
Modified Misgav-Ladach	Transverse Sharp Higher than Pfannenstiel or opened at the level of the Pfannenstiel incision for cosmetic reasons	Not specified	Blind thrusting movement of the open scissor-tip	Not specified	Visceral peritoneum not opened	Transverse Lower segment Blunt
Traditional vertical	Vertical Sharp	Vertical Sharp	Vertical Sharp	Blunt or sharp separation	Longitudinal sharp	Transverse Lower segment Blunt or sharp

Table.1.2: Types of closure of tissues in different techniques of caesarean section (From the Reproductive Health Library). [29]

Technique	Uterus	Peritoneum	Rectus sheath	Subcutaneous layer	Skin	Other
Pfannenstiel	Two layers Continuous	Both layers closed Continuous sutures	Continuous or interrupted sutures	Not specified	Interrupted or continuous	
Pelosi-type	Single layer Continuous	Not closed	Continuous sutures	Interrupted sutures if needed	Staples	Bladder not reflected inferiorly Spontaneous delivery of the placenta
Joel-Cohen	Interrupted	Not closed	Continuous sutures	Not specified	Not specified	Bladder reflected
Misgav-Ladach	Single layer Continuous	Not closed	Continuous sutures	Not specified	Two or three mattress sutures	Placenta removed manually Uterus exteriorized for closure
Modified Misgav-Ladach	Single-layer non-locking continuous sutures, or closed with two non-locked sutures layers	Not closed	Continuous sutures	Not specified	Subcutaneous suture or various skin closure methods	
Traditional vertical	Single layer or two layers Continuous or interrupted	Both layers closed Continuous sutures	Continuous or interrupted sutures	Interrupted sutures	Interrupted or continuous suture	Bladder reflected inferiorly

1.4. The pathophysiology of post-operative pain

Pain is a sensory-emotional experience.[34] It originates from external noxious stimuli from the environment that cause a localised sensation in a part of the body, to which the individual's response will be to terminate or escape the source of the stimulus. Acute post-operative pain and hyperalgesia is associated with peripheral and central sensitisations.[35] In peripheral sensitisation, the peripheral, small diameter, non-myelinated, afferent neurons lower their response threshold, increase the magnitude of response and also increase spontaneous activity .[36] The neurons, A delta and C fibres, are stimulated by inflammatory mediators like hydrogen ions, noradrenaline, bradykinin, potassium ions, histamine, prostaglandins, purines, cytokines, leukotrines, nerve growth factors and neuropeptides. [37] After peripheral sensitisation, impulses are sent to the central nervous system. This is central sensitisation, when the transformed pain signals are increased in intensity.[38] Central sensitisation occurs when the dorsal horn neurons in the central nervous systems are stimulated by the insult to tissues. Action potentials are generated by activation of calcium channels in the cell membranes by specific proteins that respond to various stimuli, such as changes in temperature, pressure or acidity. Changes in pH are found during inflammation and ischemia of uterine and skeletal muscles. The proteins that are involved in this acidic condition are mediated by the Acid Sensing Ion Channels (ASICs). [39]

1.4.1. The physiological response of the body to painful stimuli

The body responds to pain physiologically by involving most systems of the body.[40] The endocrine and metabolic response to surgical trauma starts intra-operatively, by activation of a sympathetic nervous mechanism that leads to, amongst other things, hyperglycaemia, lipolysis and protein degradation. This stress response shows clinically

as tachycardia, hypertension, and renal function impairment. Epidural analgesia with local anaesthesia obviates this response.[40]

The respiratory response is due to many factors. Uncontrolled pain impairs the sub-phrenic nerve and diaphragmatic activities, as well as voluntarily inhibiting breathing activity. There is less diaphragmatic descent and reduced lung volumes secondary to the decrease of output from phrenic motor neurons.[41] The decrease in pulmonary functions may be made worse by the administration of opioids. In addition, anaesthetic agents impair central control of breathing and depress activities of the respiratory muscles. This results in the loss of coordination of respiratory muscle activity, thereby leading to sub-optimal lung functions.

Ileus is a common occurrence post surgery caused by a combination of surgical stress and pain, mediated by sympathetic hyperactivity. The reduced gastrointestinal motility is a result of many factors. Local inflammation, spinal, supraspinal and adrenergic response can initiate inhibition of neurogenic pathway.[41] Systemic or epidural opioids can aggravate an ileus.

The cardiovascular system responds with an increase in catecholamine and sympathetic activity causing tachycardia, hypertension and generalised vasoconstriction. Of concern is the sympathetic activities on the cardiac muscles that can increase oxygen demand, and in previously cardiac compromised individuals like the elderly, may lead to angina dysrhythmias with the possibility of generating areas of cardiac ischemia. The sympathetic stimulation may generate hyper-viscosity which may lead to coronary thrombosis, in turn translating into further myocardial ischaemia.[41]

Acute pain may also result in impairment of cognition. The mechanism post-operative cognitive dysfunction is postulated to be due to dysregulation of central neurotransmitters in the cerebrum. The effect is further mediated by factors such as type of surgery, intra-operative anaesthetic or analgesic medications, post-operative analgesia

and patient's age. Imbalance in the centrally acting neurotransmitters, such as cytokines, serotonin and acetylcholine, may play a major role. Surgeries involving the heart tend to produce micro-embolism that may cause cerebral vascular microthrombi and decrease cerebral perfusion - causing delirium and impaired cognitive function.[40, 41]

The immune system, both cellular and humoral, is suppressed partly due to the release of glucocorticoids and pro-inflammatory tumour necrosis factor, interleukins and cytokines.[40] Cytokines released intraperitoneally may lead to immunosuppression which may be a factor in occurrence of peritonitis in open laparotomy. Laparoscopic surgery that involves less tissue manipulations will therefore have fewer complications.

Another response to post surgical acute pain is initiation of hypercoagulability. This is mediated by stasis, vascular injury and the formation of thrombus and is associated with an increase in tissue factor and plasminogen activator. The process is maintained or propagated with clot formation and stabilisation.[41]

For effective post-surgical analgesia, interventions at the levels of peripheral sensitisation, mediators and central sensitisation requires a multimodal approach to pain relief. In addition to local anaesthetics, other interventions that may be used as part of a multimodal approach include the following:

1. *Opioids:* Post-operative pain management is centred on opioids, although side-effects are common. Administration is best via infusion pump as patient-controlled analgesia.

2. *Non-opioid analgesics*: These act in synergy with opioids and have fewer side-effects. Examples are cyclo-oxygenase inhibitors, alpha-2 agonists, nitric oxide and N methyl–aspartate.

3. *Non-steroidal anti-inflammatory drugs*: NSAIDs inhibit prostaglandin synthesis. The platelets and gastrointestinal side effects are affected by cylooxygenase isoenzymes (COX-1).

4. *Other analgesics*: These includes clonidine, an alpha-2 agonist, nitric oxide inhibitors, acetaminophen and ketamine (N-methyl D aspartate blocker-NMDA). [40]

1.4.2. Chronic pain

There may be a higher incidence of chronic pain in sub-optimally managed acute pain, in procedures where major nerves were severed, as in thoracotomy and amputation, and in patients who experienced uncontrolled pre-operative pain. Chronic pain may be attributable to central desensitisation and NMDA sensitisation. Drugs that have NMDA antagonist properties like ketamine and methadone may be useful in preventing chronic pain, however clinical studies have shown conflicting results.[42]

1.5. Local anaesthetics

1.5.1. Evolution of local anaesthetics

In many cultures around the world, the concept of pain in medieval times and up to the early nineteenth century, was that of an original sin that needed to be encountered, and the ability to endure it was seen as a sign of willpower and virilism.[43] A nomadic tribe in Northern Nigeria, up until the present, considers withstanding pain from lashes of the cane as a sign of masculinity and as a prerequisite for marrying.

In the course of daily work, dentists were confronted with challenges of how to reduce pain. It is no surprise that they were the pioneers of anaesthesiology; Horrace Wells used nitrous oxide in 1844, and William Morton used ether in 1846. Coca leaves were first documented as herbal medicine by Vespucci in the fifteenth century. Much

later with the advent of modern chemistry in 1860, a German chemist, Albert Nieman, isolated and named cocaine in its alkaloid form, from erythroxylum coca, (coca plants) that were brought to Europe by Von Scherzer, an Austrian in 1850. Cocaine was the first local anaesthesia used in modern clinical medicine by Koller (German), in 1884. He applied it on the eye during ophthalmic surgery.[44] The news of the success of this intervention sparked the experimentation of cocaine as a local anaesthetic in other regions of the body and wider anecdotal applications. It did not take long before the realisation that the toxic effects led to addiction and even death - not only among the patients but also medical staff.

Subcutaneous injection of cocaine became popular with the invention of hypodermic needles by Francis Rynd in 1845. High concentrations of about 10-30% were used, side effects were devastating and even many physicians like Sigmund Freud, a friend of Koller, fell victim to the use of cocaine.[44] Negative publicity on the toxic side effects of cocaine, resulted in practitioners using lower concentrations of the subcutaneous injection. Amongst those who advocated a lower concentration were Haste and Reclus in 1885 who used very low concentrations of between 0.1 and 2%.

Despite the reduction in the concentration of cocaine, the search for a safer alternative to cocaine commenced in 1904 when a German scientist, Einhorn, developed novocaine (which was later called procaine in America). It was put it into clinical use by Braun in Germany. However, the drawback with novocaine was the relative weakness and the need to combine it with a high concentration of adrenaline. In addition, allergy was a major side effect. Stovaine was synthesised in France by Fourneau around the same time. Due to a series of adverse effects, search for safer products continued. Cinchocaine (Nupercaine, dibucaine) was synthesised in 1925 by Meischer, and introduced for clinical use in 1930. This was closely followed with synthesis of amethocaine (pontocaine, tetracaine) in 1928-1932 as a safer alternative, developed by Lofgren and Lundqvist and, between

1943 and 1945, at the peak of the Second World War, lidocaine was developed. Lundqvist started by experimenting on his own toes. Lidocaine is less allergenic, safe and has a stronger anaesthetic effect than novocaine. The amide type of local anaesthesia was later developed between 1957 and 1972 when drugs such as mepivacaine (synthesised by Ekenstam and Egner), bupivacaine (synthesised by Ekanstam, 1957 and in clinical use by Widman and Telivuo in 1963), prilocaine (synthesised by Lofgren in 1959 and in clinical use by Wielding, 1960), and etidocaine (synthesised by Takman, 1971 and in clinical use by Lund 1972) were introduced. Drugs, such as ropivacaine (synthesised in 1957 by Ekenstam and clinical introduction only in 1997), with few and rare side effects, are now available. Levobupivacaine was commercially prepared in the early 1990s and clinical used during 1995-1998. [44, 45.46]

1.5.2. Pharmacology of local anaesthetic agents

Local anaesthetics are made from an aromatic lipophilic ring, a hydrocarbon link, made of either an ester or an amide, and a terminal hydrophilic amine group. This is depicted in Figure 1.2.[47] The characteristics or properties of local anaesthetics are mostly determined by changes in the middle link. The amide group [-NH-CO-] are mostly metabolised in the liver, such as lidocaine, prilocaine, bupivacaine, ropivacaine, levobupivacaine and mepivacaine. This group is more widely used in clinical practice. The ester group, such as cocaine, procaine and chloroproccaine, is made of the [-O-C-O-] link and are essentially metabolised by plasma cholinesterase - hence more allergic reactions occurred in the ester group.[48]

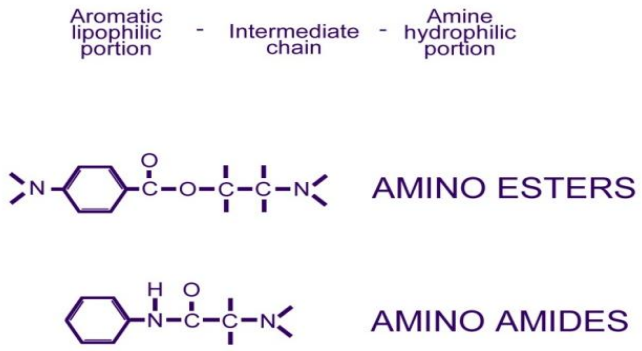

Fig. 1.2. Chemical structure of local anaesthetics.[47]

The mechanism of action of local anaesthetics is at the level of the cell membrane where it blocks inward transfer of sodium through the ionophores during the period of depolarisation. The ionophores or channels are cell membrane proteins that are important in activation and propagation of action potentials in the nerve endings. Other ion channels like calcium and potassium may also be blocked. Local anaesthetic (LA) injection is in acidic form. When injected, the perineural environment, which is alkaline, changes it to a base which is lipid soluble. The base form allows crossing the axolema, and when it gets intracellular into the axoplasm, it re-ionises into the active form for its activity.[48]

The potency of LA is directly proportional to its molecular weight and lipophilicity; the onset of action of LA is dependent on its lipid solubility and the pKa. The higher the solubility and the lower the pKa, the faster the onset of action.[49] pKa is the negative logarithm of the ionisation (dissociation) constant (Ka) of an acid. The latter is a measure of the acidity of a solution i.e. the pH of a solution in which half of the acid molecules is ionised. LA that has a higher affinity for protein binding has a longer period of efficacy. The duration of action in younger patients is shorter than in older patients. The order of loss of nervous function is pain followed by thermal, tactile, and finally motor loss. Myelinated nerve fibres (axons of neurons that are covered with lipid and protein insulating

materials) are more readily blocked than those which are non-myelinated. Smaller nerve fibres are more responsive to LA block than larger ones.[48]

1.5.3. Side effects of local anaesthetic agents

Apart from the blocking of sodium ionophores by local anaesthetics, it equally blocks K, Ca and K ion channels. It also binds enzymes, B adrenergic and nicotinic acetylcholine receptors. This explains the many side effects and adverse reactions.[48]

Ester group LAs, are rapidly hydrolysed by plasma pseudocholinesterase. This is the basis for their reduced risk of systemic toxicity compared to the amide group. High levels of LA in the plasma may inhibit the CNS pathways by manifesting as tongue numbness, light-headedness, dizziness, visual disturbances, tinnitus and sometimes disorientation. If unmanaged, more serious and life threatening side effects of convulsions, CNS and respiratory depression may supervene, eventually resulting in cardiac arrest.[50] Bupivacaine is more cardiotoxic compared to ropivacaine, because the former binds more strongly and longer to the sodium, calcium and potassium cardiac muscle ionophores. Symptoms of cardiovascular toxicity start with hypertension and tachycardia and if not managed, vasodilatation and negative ionotropic actions ensue, invariably leading to hypotension with accompanied arrhythmias and cardiac arrest. Inadvertent injection into the blood vessels may result in CNS toxic symptoms as true allergies are not common. Preservatives may be a source of true anaphylaxis. True allergies, when they occur, are more likely to be an ester group. This is due to the formation of para-amino benzoic acid, a metabolite of esters (amide group is metabolised by hepatic enzymes). The CNS is more susceptible to LA toxicity than the cardiovascular system. [51, 52]

1.5.4. Managing adverse reactions and toxicity

Most adverse reactions are mild and are allowed to run its course as it rapidly terminates. Further administration of the agent should cease. Management of adverse reaction is supportive. The airway is maintained and intermittent positive pressure ventilation is given, if necessary. Convulsions are managed by diazepam, thiopental, propofol or succinylcholine with ventilation. Hypotension is managed with fluid therapy and adrenalin. If cardiac arrest supervenes, adrenalin, intravenous lipid or a cardiopulmonary bypass are options of management.[53]

1.5.5. Common local anaesthetic agents

Cocaine

An extract of erythroxylon coca, called cocaine, is the only naturally occurring local anaesthetic. Cocaine causes vasoconstriction in low concentration and vasodilatation in higher concentration, it is therefore unnecessary to add vasoconstrictors for mucosa topical use. Cocaine is currently useful as a mucosal anaesthetic prior to endotracheal intubation in nasal surgery. It is resistant to catabolism by plasma cholinesterase, a feature that potentiates its toxicity .Cocaine is a common drug of abuse and this limits its use in clinical medicine. [51, 55, 56]

Lidocaine

This local anaesthetic is widely used in view of its rapid onset of action, and moderate duration of action and potency. When administered at normal dosages, it may be neurotoxic. Duration of action may be up to 3 hours in some instances. Lidocaine non-anaesthetic use includes intravenous administration in ventricular arrhythmia and in chronic pain syndrome [56, 57].

Mepivacaine

A hybrid of the xylidine ring of lidocaine and piperidine ring of cocaine was developed called mepivacaine. It has lower vasodilatory activity and a longer duration of action compared to lidocaine. When a vasoconstrictor is added, a significantly longer duration of action is achieved. It is widely used in dental surgery. [56]

Prilocaine

Of note in prilocaine is the possibility of induction of dose dependent methemoglobinaemia. This appears to limit its use despite the high level of pulmonary metabolism resulting in low plasma concentration. The latter is useful in that the property makes it relatively safer as a drug of choice in intravenous usage.

Bupivacaine

Bupivacaine local anaesthetic agent is exceedingly popular. The methyl tail of the piperidine ring of mepivacaine is substituted by the butyl ring, a property that enhances its longer duration of action. It is widely used in obstetrics as a neuronal analgesia. With the development of levobupivacaine and ropivacaine - drugs which have safer cardiovascular profile during inadvertent intravenous injection - bupivacaine is becoming less popular.[55, 56, 57]

Levopubivacaine

This is an enantiomer of bupivacaine. Levopubivacaine has similar potency and duration of action as bupivacaine. It has a reduced cardiotoxicity compared to bupivacaine hence a better safety profile in clinical situations when high level of LA is required.[55, 56]

Ropivacaine

The vasoconstrictive property of ropivacaine might explain the reduction in its cardiovascular toxicity. It is an S-enantiomer of the homolog of mepivacaine and bupivacaine. Ropivacaine potency and duration of action is comparable to bupivacaine, but with a better safety in the cardiotoxic margin demonstrated in many animal experiments and human studies. [55, 56]

Drugs that are commonly used with local anaesthetic agents

Combination of LA with other agents serves to either spare the dosage of LA needed, or to act as an adjunct, thereby improving efficacy, prolonging duration and decreasing unwanted side and adverse effects. Such drugs may be vasoconstrictors, alpha 2 agonists, bicarbonates, antioxidants or antimicrobials.

Adrenaline is naturally produced by the adrenal medulla and has effects on both alpha and beta adrenergic receptors. In view of its potency, a dose that is beneficial in causing vasoconstriction and prolonging the duration of action without causing significant side effects, is used (usually 1:200,000 or 5 microgram/ml).The side effects of adrenaline often occurs with inadvertent intravenous injection, manifesting as tachycardia or sometimes bradycardia when beta adrenergic blockade occurs. Adrenaline can also cause local side effects of terminal artery vasoconstriction. When adrenaline is exposed, it loses its potency rapidly. The addition of sodium metabisulfate, an antioxidant, is necessary for prolongation of its shelf life. [56]

Clonidine is used in combination with LAs as an additive, to potentiate and prolong the effect of LAs especially in postoperative analgesia. The addition of bicarbonates in doses that cannot precipitate the LA can also prolong

and potentiate its activity by increasing its pH. Antibiotics (methylparaben) are only added for use in wound infiltration. [56]

New anaesthetic agents are currently being developed. A longer acting derivative of lidocaine, called tonicaine, is being studied. Sameridine, a compound that has LA and opioid receptor agonist properties, is being researched. There are naturally occurring neurotoxins such as tetrodotoxin and saxitocin which block sodium ion channels. Manipulating liposomal and polymer delivery systems may enhance longer duration of action of local anaesthetics. Decreasing the side effects profile of LA is paramount in development of an ideal LA by manipulating the molecular structure to target specific receptors. [51]

1.6. Measuring outcomes of pain management

The current norm in clinical practice is the need to measure the outcomes of intervention in an evidenced based format. Pain management is no exemption to this principle. However, as pain is a sensory-emotional response to a noxious stimulus, measurement is subjective. Tools are needed to accomplish this measurement and must be valid for a population group, consistent and reproducible. [58]

1.6.1. Pain measuring tools

Means of measuring pain can be classified broadly into unidimensional simple scales and multidimensional complex scales. Instruments to be used for pain measurements should be suitable for a specific clinical circumstance, specific patient groups and the availability of personnel to administer the tool. A simple unidimensional pain scale may be suitable for a busy practice, an elderly patient or an ill patient who can

comfortably describe the pain in a simple format instead of a cumbersome and more detailed pain assessment questionnaire, such as the multidimensional pain scale. [59] The common simple pain scales are as follows:

Unidimensional pain scales

Verbal rating scale (VRS)

A verbal rating scale involves a simple questioning of grading pain from verbal categorical adjectives of no pain, mild pain, moderate pain or severe pain, for example. This is of advantage for the very ill or elderly who can easily categorise the pain instead of completing a whole body complex format. The disadvantage is the limited choice of the descriptive words that may not best describe the patient's feeling. For example, a common format is to describe pain as 'mild, moderate and severe' that lacks defined description. It yields categorical data and if levels of pain are just three, chi square or exact tests can be used for statistical analysis. If there are more than three levels, a more complex statistical analysis, like a non-parametric test, can be used.[58.59]

Numerical rating scale (NRS)

This is a horizontal line marked 0 to 10 with 0 being no pain and 10, worst pain imaginable (Fig. 1.3). This scale can easily be self administered and data recording is simple. It produces non-continuous categorical data like the verbal rating scale. [58]

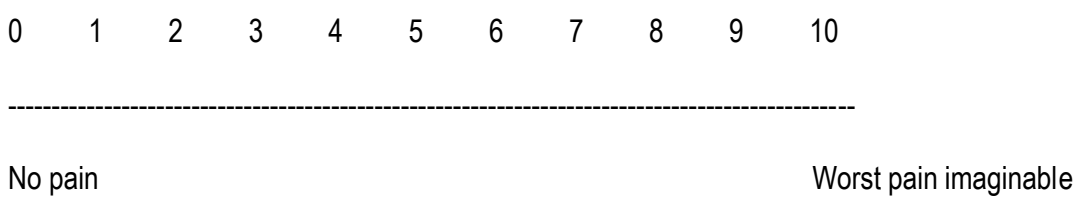

Fig. 1.3. Numerical rating scale

Visual analogue scale (VAS)

The visual analogue scale is a single horizontal 100mm line that begins with no pain and ends with worst pain imaginable.[58] The VAS is an efficient tool for pain measurement as the patient can visually estimate the point on the line where the level of pain lies. The VAS is more sensitive in representing the level of pain although it is more labour-intensive and difficult to administer to children and elderly. It generates continuous data making statistical analysis simpler to perform and can also be used to measure other emotional responses that come with pain like anxiety levels and depression. [60, 61]

Fig. 1.4 Visual analogue scale

Multidimensional scales

Unidimensional pain scales assess pain without considering the multiphase response to injury. They do not assess the patient's functional impairment, quality of life and effect on patient's daily activity. These are what multidimensional pain scales address, which are therefore more useful in chronic pain evaluation. [58, 62] Some examples of multidimensional tools are mentioned below.

The McGill Pain Questionnaire

This questionnaire assesses pain intensity and quality in relation to sensory, affective and evaluative dimensions. This reliable tool includes the patient's perception and distribution of pain. It also incorporates the numerical rating

scale. The drawback of this tool is the patient's interpretation of adjectives of measurement and the complexity of the questionnaire. A short format was created to circumvent the issue of complexity by Melzack in 1987. [58, 59, 67]

The Brief Pain Inventory

This is a multi-dimensional tool that assesses pain intensity and impairment in daily life function and is mostly used for assessment of pain in oncology. [61, 68]

Emotional tools

Pain does bring about emotional changes which can be measured in addition to the unidimensional tools. Anxiety, depression and anger are some of the emotional response to the pain complex that may need assessment. Tools such as Zung depression score; Beck Anxiety and Depression Inventories are examples. [58, 59]

Quality of life assessment

This form of tool assesses the overall impact of pain in all areas of a patient's life. A short format is available that assesses the patient's emotional, mental and social functions apart from assessment of pain. This tool is cumbersome and may not be reproducible. [58, 59, 61]

1.6.2. Post caesarean section pain assessment in obstetrics research

Pain assessment is fraught with challenges as it is a personal and subjective experience, filled with emotions; therefore it is difficult to evaluate. This explains the reason for the existence of the numerous tools designed for its assessment. There is no ideal tool; a functional tool that fits into a particular clinical situation, which is easily

administered by care givers and simple and easily understandable by the patient, will suffice in both clinical and research situations.[61] Specifically in post-caesarean section research, both unidimensional and multidimensional pain tools have been used for pain assessment. A study on 59 patients randomised to local anaesthetic ilioinguinal/iliohypogastric nerve block versus placebo used the one-dimensional scale of visual analogue score for pain measurement [62.] Another study that randomised 30 women who had caesarean section performed under regional anaesthesia into saline, ropivacaine and diclofenac used visual analogue score and opioids comsumption for pain measurements.[63] An earlier study by Ganta in the 1990s, randomised 62 women into local anaesthetic abdominal wall nerve block compared to placebo, used visual analogue pain score as an outcome. [64] Many other studies on post caesarean section analgesia using adjuvant local anaesthetics, used the visual analogue scoring tool for outcome measures.[65, 66, 69.]

The choice for visual analogue score as a measuring tool in these studies and many more may appear to be the ease of administration and its reproducibility. Multidimensional tools, for example McGill pain questionnaire [67] and its modifications, have equally been used in measurement and characterisation of post-caesarean section pain. This approach gives a dimension of quality of post caesarean section pain. A descriptive study of 60 women who underwent caesarean section had postoperative pain assessed with numeric pain rating scale and modified McGill questionnaire. Limitations of physical activities were equally measured with specific instruments.[68]

None of these trials reported any technical difficulty in the pain measurement tools that were used. It thus appears that the application of unidimensional or a combination of unidimensional and multidimensional pain tools for post-caesarean section pain assessment is practicable and reproducible, even though unidimensional assessment is more popular.

1.7. Management recommendations for post-caesarean section pain relief

Post-caesarean section pain management should be a multimodal strategy to minimise pain thereby encouraging a positive experience post-delivery and enhancing early bonding between mother and baby. Recommendations from various anaesthetic bodies have been published, but the principles remain the same: multimodalism. Below is a summary of the Royal College of Obstetricians and Gynaecologists (RCOG) and National Institute for Clinical Excellence (NICE) guidelines: [8]

Intrathecal analgesia

Diamoprhine is the drug of choice for intrathecal analgesia. Side-effects include nausea, vomiting and general body pruritus. A randomised trial involving 40 women, comparing morphine to diamorphine, showed there was no significant difference in the visual analogue scores for pain and total morphine consumption between the two groups, however the visual analogue scores for itching and drowsiness were higher in the group that received morphine.[69]

Patient-controlled analgesia

Women may be offered patient controlled analgesia (PCA) via an intravenous infusion pump or via an in situ epidural pump. Different drugs have been compared in efficacy, speed of onset and patient satisfaction. A randomised controlled trial (n=77) compared morphine via an infusion pump device to morphine combined with alfentanil. No significant difference was found, either in the overall satisfaction or grading, for the duration of analgesia. However, the speed of onset of analgesia was faster in the group that had morphine combined with alfentanil. [70]

Wound infiltration with a local anaesthetic

Pre- and post laparotomy wound infiltration, sometimes with abdominal nerve blocks, has come up in the last two decades, often with conflicting results.[71] A systematic review of 26 randomised clinical trials (n=1211), was carried out in a range of procedures during laparotomy in general surgery and gynaecology (hysterectomy). There were many clinically non-relevant outcomes, and in many others, results were negative. There atre severeal reasons that could be attributed to this inconsistent results. The review excluded studies that had peritoneal infiltration or instillation and abdominal nerve blocks. It included quasi-randomised trials and were of diverse methodologies using different interventions, dosages and different procedures in general surgery and gynaecology. Trials in this review that had local anaesthetic infiltrated above and below the rectus sheet showed positive outcomes than in those who had only subcutaneous infiltration. The question of peritoneum and above and below the rectus sheet infiltrations were addressed in the thesis by infiltrating the whole of the abdominal wall. The negative outcomes, in many of the trials, were attributed to type II errors. Also, many of the negative trials had no power calculations. To circumvent this problem, the clinical trial that was conducted to investigate the efficacy of local anaesthetic in caesarean section wound in this thesis, ensured an adequate sample size. Many of the studies that were of positive outcomes, in this review, had high methodological qualities. [71]

Non-steroidal anti-inflammatory analgesia

Many clinical trials have noted the opioid sparing effect of non-steroidal anti-inflammatory drugs (NSAID) in management of post-caesarean section pain. A randomised controlled trial (n=50) compared the rectal administration of diclofenac to placebo post caesarean section. There was no significant difference in the visual analogue scores, however, the time to first analgesic request was prolonged in the treatment group compared to placebo. [69] Another trial (n=45), in which the outcome included the amount of opioid used via a patient-

controlled epidural anaesthesia, consumed less opioids in groups that had rectal non-steroidal anti-inflammatory drugs compared to the control group. There was no difference in the visual analogue scores. [69]

The summary recommendation by the Royal College is a combined multimodal strategy of intrathecal or epidural diamorphine, post caesarean section patient-controlled epidural or infusion analgesia and a non-steroidal anti-inflammatory drug, if there are no contraindications. [8]

In South African obstetrics practice, these options are available in private health care institutions but are not readily available in most government establishments. This may be due to a dearth of expertise and the cost involved. In the public health institutions, intrathecal spinal block is usually followed by intermittent intramuscular opioids, paracetamol and non-steroidal anti-inflammatory drugs per recta or per oral.

Research recommendations

The Royal College guidelines state that further research is needed to determine the effect of wound infiltration with local anaesthetic at caesarean section on the need for post-caesarean analgesia.[8] This recommendation is addressed in this thesis.

1.8. Indications for general anaesthesia for caesarean section

There are still some indications for caesarean section under general anaesthesia in the contemporary obstetrics practice, even though it is becoming less common with the availability of better anaesthetic skills.

Maternal request for general anaesthetic caesarean is common. A hospital in Singapore had a 25% caesarean delivery rate over a twelve month period of which 20% was performed under general anaesthesia; a high percentage of which was due to maternal request. Sixteen percent of the general anaesthetic procedures performed were due to epidural failure. [72] Other indications are severe foetal distress, pregnancy induced hypertension with haematological derangement, recently administered anticoagulant, and history of adverse or allergic reaction to local anaesthetics. Maternal hemodynamic instability, cardiac diseases with poor compensation, sepsis along the skin over the vertebrae or generalised sepsis, neuro-muscular conditions such as myasthenia gravis and scoliosis were also documented indications. [73]

Prevention of mother to child transmission of HIV (vertical transmission) is an important indication for performing a caesarean section. Prevention of vertical transmission has been an important intervention in controlling the pandemic. Caesarean sections have played a major role in this regard, especially in the affluent communities globally. Any review on caesarean section techniques, may not be complete without mentioning the ever increasing rate of operative delivery as a result of strategy of prevention of vertical transmission by offering elective caesarean section.

In the 1990s, many small studies were carried out on prevention of vertical transmission of HIV infections in newborns but with conflicting results from being beneficial [74] to no benefit [75] and to non significant effects.[76]

A meta-analysis of fifteen prospective studies carried out by The International Perinatal HIV group in 1999, involving 8000 mother-child pairs was done. The findings showed a decrease in the transmission rate of about 57% after adjusting for other confounding variables like antiretroviral treatment, in women who had elective caesarean sections. Mother–child pairs, who had antiretroviral drugs during pregnancy, labour and to the

newborns, had a transmission rate of only 2% [77]. When monotherapy was changed to multitherapy, elective caesarean section, and non-breastfeeding for vertical transmission prevention, a further reduction to 1% was achieved irrespective of viral load. [78] It is of note that vertical transmission was dependent also on viral load prior to delivery; with a decrease in transmission rate in women with low viral loads.[79] High CD4 count decreases the rate of transmission.[80]

The European AIDS Clinical Society (EACS) guideline of 2008, recommended that caesarean sections be performed as prophylaxis in mothers who are HIV positive, except if the plasma HIV viral load is less than 50 copies/ml at 34-36 weeks of gestation. [81]

In the private health sector in South Africa, caesarean sections are routinely offered to all HIV positive women, irrespective of the viral load. This may be due to convenience factors especially by private obstetricians, or because of other reasons that does not allow for repeating viral load assays at 38 weeks of gestation.

1.9. Regional versus general anaesthesia for caesarean section

In centres staffed with adequately skilled professionals, caesarean sections are usually performed under neuraxail block, thereby preserving the emotional experience associated with the event, and enabling the mother to be fully awake during the birth of her child. A 2006 Cochrane Review compared the effects of regional anaesthesia with those of general anaesthesia on maternal and infant outcomes (n=1586). The maternal hematocrit was higher in patients who underwent regional anaesthesia compared to general anaesthesia and the estimated blood loss was lower in the regional anaesthesia group, although there was no significant difference between the groups in the need for blood transfusion. With regard to neonatal outcomes, one-minute Apgar

scores favoured the regional anaesthetic group but this difference was not deemed clinically relevant. [82] Participants in the comparison groups reported similar levels of satisfaction.

Thus there was no overall advantage in favour of either regional or general anaesthesia for caesarean section; the decision is for the mother to make, as long as she is adequately informed of the advantages and disadvantages of each method. The availability of standard equipment and skilled personnel is also important. [83]

1.10. Intraperitoneal local anaesthesia in surgery and caesarean section

When the peritoneum is breached, nociceptive signals send impulses to the afferent pathways of the sympathetic and parasympathetic pathways. A diluted anaesthetic lavage solution of 100-300mls of 0.15% lidocaine or 0.10% bupivacaine may be poured into the peritoneal cavity during laparoscopy as adjunct to post-operative pain relief.[20] In the mid 1980s, lidocaine was used in a study on tubal ligation via laparoscopy. Following dilution of 500mg of 0.5% lidocaine in this study, the maximum level of serum concentration reached was 2.2 microgram per ml. [84] In another study of day-case laparoscopic surgery, the incidence and intensity of referred shoulder pain was reduced following laparoscopic lavage with either lidocaine or bupivacaine. [85]

Local anaesthetic infiltration may sometimes be indicated in performing a caesarean section. The communities where it has been reported are often resource constrained. Local anaesthetics only, can also be used in rare situations when other forms of anaesthesia are medically contra-indicated, as in muscular dystrophy, kyphoscoliosis and familial dysautonomia or terminally ill patients. [86-92] It has equally been used in morbid obesity. [93] The technique of infiltration generally involves infiltration of all layers of the anterior abdominal wall in a stepwise manner until the visceral peritoneum is reached. [94, 95] This knowledge that caesarean sections have

been performed using local anaesthesia, makes it logical that some form of positive analgesic effect could be achieved when local anaesthetic is used as an adjunct to post-operative pain management.

1.11. Chromatography and measurement of local anaesthetic serum concentration

The effect of local anaesthetics as an adjunct to post-caesarean section pain management is studied in this thesis. Due to the risk of LA toxicity, an assessment of serum LA concentrations following intra-peritoneal administration was deemed essential, before embarking on the clinical trial. Serum LA concentrations are measured using chromatography.

Chemical analysis was performed by separation of the constituent of a mixture. In 1903, a method of separation was invented and described by a Russian botanist, Mikhail Tswett. He separated components of a plant pigment by running the mixture through a tube filled with calcium carbonate. The pigments settled in different colour bands in the tube segment which he called chromatogram. Chromatography was derived from a Greek word meaning 'to write in colours'. Subsequently, he applied this method of adsorption chromatography to separate colourless substances. It was not until the 1930s when a German, Willstarter, popularised the discovery to the Western world. Different techniques of chromatography were developed over the century, some of which are mentioned below: [96, 97]

1.11.1. Ion exchange chromatography

Instead of using calcium carbonate as the adsorbent, electrically charged substances called zeolites were used. Synthetic resin was quite popular and was introduced by an American, Spedding for separation. It was employed in the Second World War as a component of the survival kit to get non-ionised water from the sea.

1.11.2. Paper chromatography

This was invented by Martins and Synge in the 1940s. Instead of using resins or calcium salts, porous paper strips were used as the adsorbent. The mixture substance to be separated is applied to the end of a paper strip and a solvent added. The solvent carries the mixture up the paper strip in different colours – this happens at different speeds due to the component's different physical characteristics. If it is colourless, a reagent is added to delineate the colours and each band region is cut out for further analysis. This discovery was of such major importance in chemistry that the duo was awarded the Nobel Prize for Chemistry in 1952. Paper chromatography was put into use in the discovery of structures of antibiotics, insulin and components of nucleic acid. This information was used by Watson and Crick to map out the structure of deoxyribonucleic acid.[98,99]

1.11.3. Gas chromatography

This method was invented by Martins and James and uses gas as the adsorbent to separate complex mixtures of substances, instead of using a liquid solvent. [97, 98]

1.11.4. Thin layer chromatography

This method makes use of a gel (e.g. silica, alumnia) as adsorbent, which is evenly spread on a glass surface. The procedure of separation is fast.[100]

1.11.5. High performance liquid chromatography (HPLC)

It is a form of column chromatography whereby the solvent is put under high pressure instead of relying on gravity. A faster and better separation is achieved. There are two types of HPLC, the normal phase HPLC and the reverse phase HPLC. The former is not often used. The column contains silicon particles which is ionised and the solvent is non-ionised. The ionised compounds adhere to the ionised silicon thereby allowing the nonionised

compounds to move faster and enable faster separation. In the reversed phase HPLC, the ionised silica is modified to non-ionised state by attachment of long carbon chains. This enables the ionised molecules to travel faster. It is the most widely used method. [101]

High performance liquid chromatography, in its various modifications, is used to measure serum concentration of local anaesthetics like ropivacaine.[102, 103] The process starts with ultra filtration of the sample using centrifugal filtration devices. Aliquot of the ultra filtrate is pumped through high pressure with the solvent. The output is sent to a detector for analysis. [101-103] Plasma concentrations of local anaesthetics have mostly been measured with the use of chromatography technique. Prilocaine was measured using this technique following intravenous regional anaesthesia in the 1960s.[104] Plasma concentrations of lidocaine, mepivacaine and bupivacaine were determined by high performance liquid chromatography (HPLC) [108]. Plasma concentration of ropivacaine was determined by a highly selective and sensitive method of HPLC and mass spectrometry [106]

1.12. Deductions from the literature review and gaps in knowledge

Local anaesthetics are proven to offer potent pain relief. Their role as adjuvant postoperative pain relief has been accepted by some surgeons and rejected by others as noted earlier in this review of literature. What is needed is a summary of eligible randomised trials to guide clinical practice. This has been lacking over the decades and is justifiably explored in this thesis.

Most obstetricians, who believe in the value of local anaesthetic (LA) wound infiltration, inject the LA subcutaneously. However, the peritoneum is capable of generating deep-seated and diffuse pain when breached. The hypothesis of this thesis is that by wholly infiltrating all the anatomical layers of the anterior abdominal wall, including the peritoneum, better analgesia will be achieved. To my knowledge, there are no randomised clinical trials that have compared LA to placebo, using this technique of infiltration.

Furthermore, little is known about the serum concentrations of LA following intraperitoneal administration or the risk of toxicity with this method of LA administration. This obvious gap in knowledge supports the need for the serum concentration study of LAs, following peritoneal infiltration and spraying, that forms part of this thesis.

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CHAPTER TWO

ROPIVACAINE ABDOMINAL WOUND AND PERITONEAL INFILTRATION IN POST-CAESAREAN SECTION PAIN RELIEF – A RANDOMISED CONTROLLED TRIAL

Synopsis

This chapter explores the effect of local anaesthetic compared to saline placebo for wound infiltration in women undergoing general anaesthesia for caesarean section. Ropivacaine was chosen in view of its relative safety. A double-blind, randomised placebo-controlled study, with adequate sample size and analysed based on intention to treat, was conducted. An innovative technique was used whereby the peritoneum was infiltrated or needle-sprayed with local anaesthetic. Ropivacaine wound infiltration to all layers of the anterior abdominal wall, including the peritoneum, reduced post-operative pain and need for additional post-operative opioids.

2.1. Materials and methods

2.1.1. Ethics Approval

This study was approved unconditionally by the Human Research Ethics Committee of the University of the Witwatersrand in June 2006 (Protocol Number MO60623).

2.1.2. Hypothesis

Ropivacaine wound infiltration into all layers of the anterior abdominal wall and infiltrating and spraying of the peritoneum, will decrease post operative pain and reduce rescue analgesic requirement in the immediate post caesarean delivery period.

2.1.3. Intervention

Treatment group: Patients who consented to participate in the trial that were randomly allocated to receive 7.5 mg per ml of ropivacaine (30 mls volume).

Control group: Patients who consented to participate in the trial that were randomly allocated to receive placebo of equal volume.

2.1.4. Recruitment

Power calculation: In July 2006, a small pilot trial involving seven patients undergoing caesarean section under general anaesthesia was carried out. All patients needed rescue opioid within one hour of delivery. For the purpose of sample calculation, it was estimated that 90% of women in the placebo group would require pethidine within an hour. Thirty eight women in each group were needed to show a reduction from 90% to 60% in the intervention group. (Alpha = 0.05, beta = 0.20. Power = 80%) (Epi-Info software, 2002). To compensate for possible loss of data, 50 women were randomised into each group.

Period of recruitment: In the period between 2003 and 2005 in my obstetrics practice, the average number of deliveries per month was 30 women by both caesarean section and normal vaginal births. This amounted to about 360 deliveries per year. In this practice, as in many private obstetrics practices in South Africa, about 50% of the deliveries were by caesarean section. It was projected that 180 patients would have had a caesarean section in a 12 month period. With an assumption of 50% patients agreeing to participate in the trial, it would take approximately 13 months to complete recruitment of 100 patients for general anaesthetic caesarean section. Recruitment started in August 2006, and ended in December 2007 (a 17 month period). (Figure 2.1). Ten more patients were recruited for the pharmacokinetics trial.

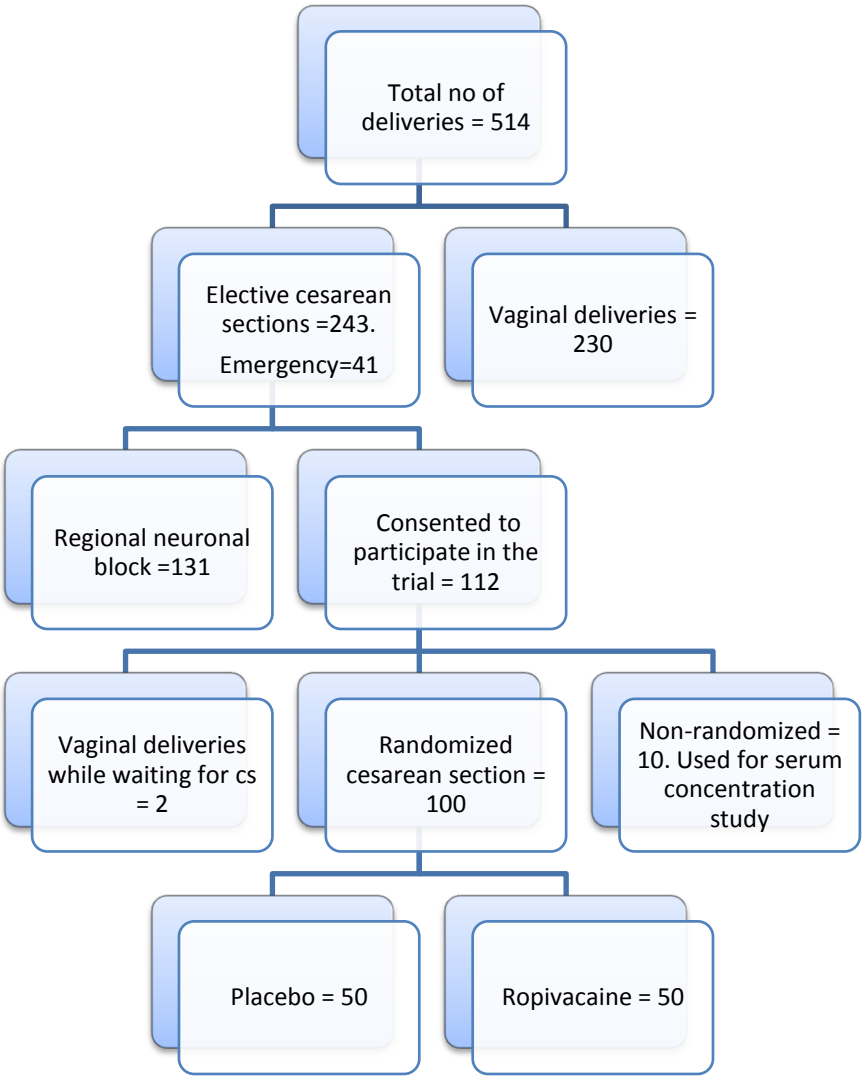

Fig. 2.1 Flow chart for patients recruited and delivered during the 17 month period of the trial

Inclusion criteria: Participants were 18 years old or more, attending an antenatal clinic with single pregnancies, were asked to participate in the trial at about at 34 weeks gestational age. They were without medical risk (ASA class I-II), eligible for elective caesarean section and did not have preference for type of anaesthesia - regional neuronal block or general.

Exclusion criteria: Patients who failed to give their consent, a history of previous local anaesthetic events, severe hypertension in pregnancy with or without proteinuria, cardiac diseases, epilepsy and any other major medical disorder of or associated with pregnancy, breech presentation and multiple pregnancies.

Consent: The patient information leaflet was read to the patients during their antenatal visit at about 34 weeks of gestation and they were allowed to ask questions and clarify areas of concern. The leaflet was offered to the patient to take home if she wanted to further peruse the details. If the patients agreed to participate, the consent form was signed and dated. See patient information sheet and consent in appendix section (Pages 180-206).

2.1.5. Randomisation and theatre procedures

One hundred random numbers were generated using EPIINFO software by a research unit- Effective Care Research Unit - affiliated to the University of the Witwatersrand based in East London, South Africa. The theatre matron in the hospital where the trial was conducted, held the random numbers confidential, and prepared one hundred cards marked with instructions for drawing up either ropivacaine or normal saline. One hundred envelopes were labelled and the corresponding numbered card inserted. The envelopes were thereafter sealed. The random list was sealed in another envelope for safe-keeping. Each time a patient who had earlier consented to participate in the trial was brought to the theatre suite, the matron prepared the solution for injection. She wrote the patient's name against the next number on the register, opened the same numbered envelope, and drew up 30ml of either 7.5 mg/ml of ropivacaine or saline (depending on what is written on the card). She replaced the card in the envelope and placed them in a sealed container for safekeeping. She took the syringes with the solution to theatre, and squirted the contents into a sterile galley-pot, from which the surgeon drew up the solution for infiltration during caesarean section. All patients weighing 65 kg or more received the fixed dose regimen of 225mg of ropivacaine and those weighing less, received 3mg/kg of ropivacaine or equivalent volume of saline placebo. (For brachial plexus block, all women weighing 60kg or more received a fixed dose regimen of 225mg).

The clinical trial was conducted in Medi-Clinic Private Hospital, Nelspruit. This is a private hospital setup and it was impossible to use a single anaesthesiologist for the trial. The anaesthetists' group of eight specialists were consulted about the study, and used similar anaesthetic regimen to ensure uniformity as much as possible. All patients were monitored by ECG, end-tidal CO2 concentration, blood pressure and pulse rates and O2 saturation. Similar methods of induction, maintenance, muscle paralysis, analgesic and reversal of anaesthesia were used. In general, the following was suggested as routine for all cases randomised: medications used included- Thiopental sodium @ 4mg/kg, Suxamethonium 1mg/kg, Rocuronium 0.3mg/kg, Rapifen 1mg or sufental, if needed, Cefoxitin 1gm intravenously 8hrly 3 doses, Syntocinon/syntometrine 1 ampoule, Neostigmine 2.5mg and Robinul 0.2mg/ml. At the discretion of the anaesthetist, any other beneficial intervention was used as necessary, as long as it was documented.

Post-operatively, rescue Pethidine 100mg 3-4hrly and Diclofenac 75mg intramuscularly 12 hourly were used. Tramadol/acetaminophen 2 tabs 6hrly from Day 1 were used as necessary.

Surgical procedure: Patients were prepared and draped. The Pfannenstiel incision was preferred unless previous midline sub-umbilical incision was performed. A routine lower segment caesarean section was performed, baby delivered, syntocinon® 5 units given and the placenta delivered by cord traction. The uterus was closed by a single layer of inverted figure of 8 vicryl 1 suture or continuous suture. Haemostasis was secured with further single sutures. Uterovesical visceral peritoneum on the anterior uterine wall was left unsutured. Five millilitres of the 30mls of pre-prepared solution in the galley-pot, was drawn into a 20mls syringe attached to a 23 gauge needle and needle-sprayed on the unsutured peritoneal edges. The receded parietal peritoneal edges were sought for and pulled into view with several artery clamps. This was to allow visualisation that enhanced direct

infiltration of another 5 millilitres (mls) of the prepared solution into the parietal peritoneum. The parietal peritoneum was also left unsutured. The rectus muscles were approximated with 2 interrupted vicryl 1 (polyglycolic) sutures. The rectus aponeurosis edges were infiltrated with another 10 mls of the prepared solution and the edges sutured with vicryl 1 cutting needle. The remaining 10 mls was infiltrated subcutaneously along the superior and inferior skin wound edges and the skin approximated with subcutaneous absorbable vicryl 2. 0 sutures. All patients had 225mg of ropivacaine except those who weighed 64kg or less that received a volume equivalent to 3mg/kg body weight. The time of completion of skin wound closure was recorded. All caesarean sections were carried out by the same surgeon, the student.

2.1.6. Pain Assessments

Pain assessment was routine standard for Medi-Clinic post-operative patients using the numerical rating scale and the verbal rating scale. Despite this, eight Medi-Clinic employed midwifes who were on day and night shifts, were trained on pain assessments, meticulous record keeping and other requirements of the protocol. They were continuously retrained, and the ideals of conducting a proper clinical trial emphasised on a regular basis. This ensured standardisation. Taking into cognisance that this study was a double blind randomised trial, any systematic difference in pain scoring between observers should be evenly distributed between the two groups. The first pain assessment was done at 15 minutes of skin closure, in the recovery room. One hundred milligrams of pethidine was prescribed by the anaesthetist 3-4 hourly intramuscularly as necessary to all patients. Pain assessments continued in the ward for 24 hours.

If at any stage the doctors looking after the woman needed to know what the injection was (for the purpose of her care), the theatre matron was asked to ‘unblind’ the treatment and mark down on the register that the treatment was ‘unblinded’.

2.1.7. Outcome measures

The primary end-points were severe/unbearable pain at 60 minutes post-operative or need for rescue pethidine within 60 minutes post caesarean section. Secondary outcome were pain scores, oral analgesic (tramadol 32.5mg/ acetaminophen 325mg) requirement, and side effects.

2.1.8. Follow up

Fifteen minutes, 1 hour, 2 hours, 4 hours 8 hours, 16 hours and 24 hours after closure of the skin, a pain assessment questionnaire using a three-level verbal rating scale of no pain, moderate pain and severe/unbearable pain was administered. A second pain scale called numerical rating scale was administered at the same time. The visual analogue scale correlates well with a verbal 11-point numerical rating scale. [14] The 11-point pain scale ruler was routinely used in Medi-Clinic Hospital, Nelspruit with 0 as no pain and 10 as the worst pain imaginable. These simple pain scales were administered by attending midwives. The patients were shown the scale and asked to state their pain score at a particular time, from 0-10. The midwives, who were selected and have been re-trained for the trial, were told not to seek for any intervention that will unblind the allocation like touching the wound edges.

Narcotic analgesics were administered as necessary and the pain assessment questionnaire, with other information on the data collection form were completed at intervals. Most women were expected to be discharged on day two post-operative. Post surgical follow up was routinely done 6 weeks post-operatively unless wound infection supervenes or if there is any other problem which the patients were advised to report.

2.1.9. Data collection

Pre-randomisation data: Consents to participate in the trial were previously obtained during the patient's antenatal visit. (See appendix) and were clearly identified. Pre-randomisation data that included the patient's age, weight, parity and the hospital identification stickers were collected on the operation day, in the labour ward prior to the caesarean section by the investigator.

Outcome data: These were collected by the investigator, the theatre recovery nurses and the labour ward midwives. The investigator gave advice when there was a need for clarification. The outcome data included verbal rating scales and numerical rating scales, use of pethidine, rescue tramadol/acetaminophen analgesic requirement, pyrexia above 38 degree Celsius, vomiting, pruritus and wound sepsis.

2.1.10. Statistical analysis

Results were entered into Microsoft office excel 97-2003 spreadsheet and cross checked for errors. It was imported and analysed with a statistical software package, Epi-info version 3.4.3, 2007.

Data entry and checking were continuous and queries were followed rigorously to ensure that clarification was done without delay. The analysis was on an intention-to-treat principle with comparisons made between ropivacaine abdominal wound and peritoneal infiltration and placebo, for primary and secondary outcomes. Mantel Haenszel analysis method was used for comparison of dichotomous data which was expressed as percentages and relative risks with 95% confidence intervals. Comparisons of non-categorical data were by Mann –Whitney two-sample test (equivalent to chi square). Median and range of data were calculated and the degree of significance determined by p values below 0.05.

Primary outcomes of clinical study: Severe /unbearable pain within 60 minutes post-caesarean section and need for pethidine administration within 60 minutes of procedure. Secondary outcomes were verbal rating scales and

numerical rating scales, use of pethidine, rescue tramadol/acetaminophen analgesic requirement, pyrexia above 38 degree Celsius, vomiting, pruritus and wound sepsis.

2.1.11. Quality control procedures

1. Data checking and entry of completed data collection forms were meticulous. Data sheets and all other documents were stored for future reference, audits and queries.
2. Double-blinding with identical-looking placebo (saline) will avoid any bias at entry to the trial and during the monitoring of patients and assessment of outcomes.
3. Randomisation took place shortly before the patient was taken to the operating suite.
4. Good Clinical Practice (GCP) procedures (WHO 1995) were followed.
5. Data were analysed and reported on an intention-to-treat basis.

2.2. Results

A total of 2868 patients were delivered at Nelspruit Medi-Clinic obstetrics unit between August 2006 and December 2007 during the trial period, out of which the author delivered 514 patients. This represented 18% of all deliveries in the unit. Of the 514 patients delivered by the author, 284 were by caesarean section (55.2%). Of these, 243 had elective Caesarean section (47.2%). The rate of caesarean delivery in the unit by all obstetricians during the trial period was 60.3 %.

Prophylaxis against mother to child transmission of HIV was the main indication for performing elective caesarean section by the author (46.3%) (Table 2.1). The average gestational age when blood was taken for viral load counting and CD4 count was 32 (SD 6.4) weeks. The average viral load was 85,740 with the lowest load of

1,732 recorded at 38 weeks and the highest 1,300,000 recorded in a patient at 25 weeks of gestation. There were no patients who had a third trimester viral load of less than 1000. The average CD4 count was 399 (SD 265).

The baseline data are depicted in Table 2.2 and 2.3. Missing data are indicated by the N values (total of 50 women in each group).The two arms of the study, ropivacaine infiltration and saline control were comparable in respect to age, height, weight and parity. Nine women had body weight between 60kg and 65kg, five in the ropivacaine group and four in the control group. None weighed less than 60kg. Overall, there was no significant difference in the baseline characteristics.

Twenty four out of 50 women required rescue pethidine within 1 hour or experienced severe pain at one hour post caesarean section in the ropivacaine group compared to 47 out of 50 women in the saline control group (RR 0.51, 95%CI 0.38-0.69) (Table 2.4). There was a significant reduction in the numerical pain rating scale (NRS) up to 2 hours in the treatment group compared to the control [median (range) 2, (1-3) versus 2(1-10)]. (Table 2.5)

Six out of 50 patients in the ropivacaine group had severe or unbearable pain at 15 minutes post-operative compared to 31 of 50 women who had saline placebo (RR 0.19, 95% CI 0.09-0.42). The reduction in pain continued up to 2 hours postoperative. Six out of 50 patients in the ropivacaine group needed at least 75 mg of intramuscular rescue diclofenac injection in the first 24 hours compared to 30 out of 50 in the saline group. Tramadol/acetaminophen tablets consumed in the ropivacaine group were 236 versus 334 in the control group. [Median (range], 4(3-12) versus 7(4-20); p=0.001].

One patient in each group had vomiting and pruritus. No patients, out of the 49 in the ropivacaine group, had wound infection but 3 out of 50 in the saline placebo group had septic wounds. (RR 0.15, 95% CI 0.01- 2.75).

There was no cardiovascular or central nervous system event. No patients reported either overall poor pain control or poor general post-operative satisfaction. There was no need to unblind the group allocation during the trial.

Table 2.1 Indications for elective caesarean section amongst trial participants (N = 110)

Indication	n	%
Prevention of mother to child transmission of HIV	51	46.3
Mother's choice	17	15.4
Previous Caesarean (with or without HIV)	22	20
Antenatal pelvic disproportion (big baby, etc)	4	3.6
Abnormal Doppler (Reversed end diastolic flow)	3	2.7
Impaired foetal growth with oligohydramnios	3	2.7
Bad obstetrics history.	2	1.8
Severe genital warts	2	1.8
Previous vertebral operation	1	0.9
Placenta praevia	2	1.8
Previous pelvic prolapse surgery with or without use of mesh	2	1.8
Previous abdominoplasty	1	0.9

Table 2.2 Baseline data: ropivacaine versus placebo [expressed as means and standard deviations (SD)]

	Ropivacaine			Saline placebo			
	N	Mean	SD	N	Mean	SD	P value
Age (years)	50	29.66	5.26	50	30.54	6.09	0.44
Weight (kg)	46	79.52	16.76	48	79.68	14.25	0.75
Height (cm)	41	160.92	10.71	36	160.41	6.90	0.80

Table 2.3. Baseline data: ropivacaine versus placebo [expressed as proportions (n/N) and percentages(%)]

	Ropivacaine		Saline placebo		
	n/N	%	n/N	%	P value
Pfannenstiel incision	49/50	98	48/50	96	0.57
Primiparous	15/50	30	14/50	28	0.83

Table 2.4. Pain outcome data of participants: ropivacaine versus placebo [continuous data expressed as median (range)]

	Ropivacaine		Saline placebo		
Outcome	N	Median (Range)	N	Median (Range)	P value
Pain score 15min	50	1(1-3)	50	3 (1-8))	0.000
Pain score 1hr	50	2(1-3)	50	3 (1-5)	0.003
Pain score 2hrs	49	2(1-3)	49	2 (1-10)	0.008
Pain score 4hrs	50	3 (0-8)	49	5(1-10)	0.06
Pain score 8hrs	50	3(0-8)	50	3(0-9)	0.25
Pain score 16hrs	50	2(1-5)	46	2(1-4)	0.16
Pain score 24hrs	49	2(1-6)	48	2 (0-3).	0.32

Table 2.5 Dichotomous outcome data of participants: ropivacaine versus placebo [Expressed as numbers (n=no. of events, N=total number), percentages and relative risk (RR) with 95% confidence intervals (95% CI)]

	Ropivacaine			Saline placebo				
Outcome	n	N	%	n	N	%	RR	95%CI
Severe pain 15min	6	50	12	31	50	62	0.19	0.09,0.42
Severe pain 2hrs	4	49	8	13	49	27	0.31	0.11,0.88
Severe pain 4hrs	9	50	18	15	48	31	0.58	0.28,1.19
Severe pain 8hrs	10	50	20	14	50	28	0.71	0.35,1.45
Severe pain 16hrs	6	50	12	11	46	24	0.50	0.20,1.25
Severe pain 24hrs	5	49	10	6	48	10	0.82	0.27,2.50
Temp above 38	0	49	0	0	50		Not estimable	
Vomiting	1	49	2.	1	49	2	1.00	0.06,15.53
Pruritus	1	48	2	1	48	2	1.00	0.06,15.3
Septic wound	0	49	0	3	50	6	0.15	0.01, 2.75
Pain satisfaction poor (not satisfied)	0	49	0	0	47	0	Not estimable	
General satisfaction poor	0	49	0	0	50	0	Not estimable	

2.3. Discussion

Caesarean section rates in most regions of the world have been increasing. In the author's practice, during the period of this study, the caesarean section rate was 54%. The caesarean section rate performed by the entire unit in the hospital, including all obstetricians, was 60% of total deliveries. These figures are similar to the caesarean section rates in other private hospitals in South Africa. [1,2]

The most frequent indication for caesarean sections in the trial was prophylaxis against mother to child transmission of HIV. The province of Mpumalanga where the study was done had the highest HIV incidence in South Africa of 2.4 % per year in 2005. The HIV prevalence amongst South Africa pregnant population was 37% (95% CI, 24.9-51.0) in 2005 [3] - a year before the commencement of this trial.

In this clinical trial, caesarean sections done for HIV prevention of vertical mother to child transmission accounted for 46%. Most general practitioners in Nelspruit area referred HIV positive patients, who had medical insurance, for specialist assessment and delivery by caesarean section. This accounted for the high rate of HIV positive expectant patients in the practice. Many of these patients were referred after 30 weeks gestation.

An increased rate of caesarean delivery in South African obstetrics practice has followed the European and American recommendation of offering caesarean delivery in women with viral load of greater than 1000 copies per ml in the last trimester. There were no patients with undetectable viral copies that participated in the trial. This might be due to newly diagnosed HIV infected patients that presented late in pregnancy, or if earlier diagnosed, were never on antiretroviral drugs. It may also be due to poor compliance.

Patients' choice was the second highest indication for caesarean section at 15.4% in this study. The reason(s) for each patient's decision on a caesarean section was not documented in the trial. Many reasons have been attributed to the patients' choice for elective caesarean delivery without any medical reason. The fear of repeating of a previously traumatic delivery experience or outright fear of vaginal delivery amongst primigravida is a widely recognised reason. [4]

Other reasons for patients to request elective operative delivery are convenience to parents and obstetricians, prevention of perineal damage and a better reassurance for a lesser risk of morbidity to baby and avoiding pain in labour and during delivery.[5] There is much debate amongst health care givers and parents, as to whether patients should be allowed to choose how they want to be delivered. However, in most South African private obstetrics practices and also in the unit where this trial was carried out, patients' request for a caesarean section for non medical reasons is often granted as long as the obstetrician discusses the pros and cons of the procedure with the mothers.

Post caesarean section pain is mediated not only by somatic nerves but also by a visceral component. Intervention at the level of the peritoneum may increase the efficacy of analgesia and to the author's knowledge this has not been explored in the context of post caesarean section analgesia. In a study where local anaesthetic was instilled into the peritoneum after laparoscopic surgery, morphine requirement was less compared to when saline placebo was administered. [6] Extrapolating from this trial, it is reasonable to assume that sprinkling or infiltrating local anaesthetics onto the peritoneal surfaces and infiltration of the rectus aponeurosis and the subcutaneous tissue, during planned caesarean section, may alleviate post-operative pain.

The choice of anaesthesia for this study was ropivacaine. It is an agent of the amide group which has a long duration of action. The mechanism of action is through a reversible blockade of nerve impulse across the fibres by preventing sodium ions diffusion into the neuronal cell membranes.[7]

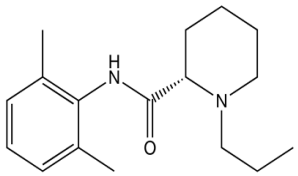

Fig. 2.2. Molecular structure of ropivacaine. (Reproduced from Wikimedia Commons)

Ropivacaine has intrinsic vasoconstrictor activities because of its' slow diffusion away from site of infiltration. For this reason, vasoconstrictors are not added to ropivacaine and the delay in local diffusion makes it a lower risk for cardiovascular side effects in the event of inadvertent intravascular injection. Due to this better safety profile, ropivacaine was used for the trial. At higher concentration, ropivacaine produces surgical anaesthesia and at lower concentration it produces analgesia. [7] Pre-incision infiltration was not considered because of the risk of drug transmission across the placenta to the foetus. Ropivacaine is becoming widely available in view of its safety, and is comparable to bupivacaine in cost.

The recommended dosage by AstraZeneca pharmaceutical limited of ropivacaine for minor nerve block and wound infiltration anaesthesia, in an adult weighing 60kg or more, is 225mg of 7.5mg/ml solution.[7] The dosage chosen for the clinical trial was 225mg i.e. three ampoules of 75mg/10ml. It is less than the 300mg maximum dose recommended at a single infiltration for major nerve block such as brachial plexus. A dose of 3mg/kg body weight was used for women weighing less than 64kg (60mg in the drug insert but 4kg added to compensate for the immediate weight loss following delivery accounted for by the foetus, placenta, amniotic fluid and blood).

A trial of 30mls of 7.5mg/ml solution ropivacaine equivalent to 225mg regardless of the patient weight has been conducted for instillation during laparoscopy. [6] Many other trials were conducted using a fixed dose regimen in surgery and gynaecology. [6, 8-14] The advantage of a fixed dose regimen will be the ease of application in a clinical setting. The site of administration and action is local, but systemic absorption and plasma concentration, which is proportional to the weight, may be of importance in ensuring drug safety. A pharmacokinetic study was performed with this regimen and the report given in chapter 3.

As alluded to earlier in the review of literature, there is still a place for caesarean section under local anaesthetic infiltration but there is no known trial on the dose of local anaesthetic to use. The anaesthetic dosage of 225mg (7.5mg/ml solution) ropivacaine used in this trial, by extrapolation, may be used for infiltration anaesthesia in patients requiring caesarean section by local infiltration only.

It is now a well accepted practice that general anaesthesia is not the first choice of anaesthesia for caesarean section, but indications do exist. Patients' preferences should be respected, [15] and certain patients may not be suitable for regional anaesthesia. The patients who agreed to participate in this trial were those who were due for caesarean section under general anaesthesia and who consented to random allocation to the study groups. According to this study, patients who were operated upon under general anaesthesia, benefitted from the infiltration of all layers of the abdominal wall and infiltration/spraying of the peritoneal surfaces, with 7.5mg/ml ropivacaine solution (225mg). The route of administration for this trial was through direct wound infiltration as opposed to abdominal nerve blocks. This makes the intervention more widely implementable, as abdominal wall nerve blocks require specialised training, bearing in mind that most caesarean sections in resource-constrained

settings are carried out by non-specialists. The simplicity of this intervention will make it widely acceptable and may change practice in many health care facilities worldwide.

The advantage of pain relief offered by complete wound infiltration and peritoneal spraying gradually diminishes as time progressed. This was not unexpected as the onset of action of ropivacaine is 1-15 minutes and the duration of action is 2-6 hours.[7] the maximum benefit in this study was seen at 15 minutes after skin closure. The amount of pethidine used in the first hour was significantly reduced in the ropivacaine group. By four hours, the difference was not statistically significant, probably due to dilution of the early effects, as the ropivacaine wore off over time. In addition, the requirements for diclofenac and tramadol/acetaminophen analgesia were reduced. The early positive effect on the need for additional post-operative analgesia may be important to facilitate bonding of the mother with her newborn.

A significant proportion of post-operative pain may come from superficial structures, but peritoneal pain may also be of importance.[16] Anaesthetising the peritoneal surfaces with ropivacaine may be partly responsible for the positive result in this trial compared to studies where only the skin and subcutaneous tissues were infiltrated with different outcomes. This assumption will need to be confirmed in a study comparing the traditional superficial wound infiltration with wound infiltration down to the peritoneum. The decision to compare the clinical outcome of local anaesthetics to all abdominal layers and peritoneum with placebo, emanated from the fact that no study, according to the author's knowledge, and as at the time of commencement of this trial in 2006, had explored and documented this approach in caesarean section analgesia. The technique is different from that in which only the skin and subcutaneous tissues were infiltrated. The finding will thus serve as a base line for comparing other clinical applications in future trials.

A secondary objective of this study was to evaluate the safety of 225mg ropivacaine - which may be used for performing caesarean section in those rare instances in which surgery is performed under local anaesthetic infiltration. There was no allergic, cardiovascular or central nervous system side effect amongst the ropivacaine exposed patients, or those that were randomised to receive placebo. It should be noted that a clinical trial of this nature, which has side effect as a secondary end result, will require far more participants than 100 patients. The small sample size is a limitation to the study. There has not been any trial, to our knowledge, that has addressed the dosage for carrying out caesarean sections under local anaesthetic infiltration. This may serve as a guide for such cases or a future trial. A lower local anaesthetic dosage, with higher volume, may be adequate in patients having caesarean sections under general anaesthesia, but this too would require further clinical study.

This trial did not evaluate events around breastfeeding as an outcome, because the indication for the majority of the patients, who were electively scheduled to have caesarean sections, was prophylaxis against mother to child transmission of Human immune Deficiency Virus (HIV). Thus most would not have been planning to breastfeed their babies.

Time of discharge was not evaluated because all patients recruited for the study paid their medical bill through the medical insurance companies. These companies normally advise on the number of days for hospitalisation. To avoid unnecessary financial burden on the patient, we strictly followed the advice of the medical insurance for suggested day of discharge, unless medically indicated, such as in cases of severe pain or wound breakdown. In this trial, there were none reported. To assess the date of discharge as an outcome for evaluating the pain relief would therefore not be of use for this study.

A sub-group analysis based on patients who had previously had their babies delivered by caesarean section, did not alter the results. The trend to performing caesarean sections under regional anaesthesia, with improvement in awareness, training and skill, will continue to increase. Meta-analysis in the following chapter showed benefit when local anaesthetic wound infiltration was used as adjunct in women undergoing regional block. It will be worthwhile to explore infiltrating local anaesthesia down to the level of the peritoneum in women with regional anaesthesia and comparing it to women who will have local anaesthetic administration to the subcutaneous and skin only. This will define the role of peritoneal administration. The same is applicable to women who have general anaesthesia.

2.4. Conclusion

Ropivacaine wound infiltration and peritoneal spraying as post-operative analgesia in elective caesarean section on single pregnancy at term, reduced the need for narcotics and non narcotic analgesics and severe pain in patients undergoing general anaesthesia. This novel and simple technique has clearly established that local anaesthetic administration to all layers of the abdomen down to the utero-vesical peritoneum is superior to placebo. This could serve as a baseline for further studies and could be used as a routine adjuvant pain-relief intervention in patients undergoing general anaesthetic caesarean sections worldwide. Use of a lesser concentration and larger volume may be worthy of further study.

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CHAPTER THREE

ROPIVACAINE SERUM CONCENTRATION FOLLOWING CAESAREAN SECTION WOUND AND PERITONEAL INFILTRATION – A PHARMACOKINETIC STUDY

Synopsis

Local anaesthetics have been employed over the decades to relieve post-operative pain. Ropivacaine wound infiltration, including peritoneal infiltration or spraying, for caesarean delivery pain relief is a new advancement. Since drugs may be optimally absorbed by the peritoneum, the peritoneal route of administration has the potential to reach toxic serum levels. No pharmacokinetic studies of local anaesthetic agents have been done with this route of administration. For this study, serum concentrations were determined at various intervals following the administration of 225mg of ropivacaine. The maximum serum concentration of ropivacaine was within safe levels and similar to levels reached following epidural caesarean deliveries.

3.1. Study objective

To determine the maximum serum concentration of Ropivacaine following administration of 225mg of Ropivacaine through all layers of the anterior abdominal wall, including the peritoneum, in patients undergoing general anaesthetic caesarean section.

3.2. Methodology

Institutional approval was obtained from the Committee for Research on Human Ethics subjects, University of the Witwatersrand in 2006. The study was carried out at the Nelspruit Medi-Clinic Private Hospital in 2007. Out of the 110 patients recruited for the clinical trial, as stated in Chapter 2, the last (consecutive) ten patients were selected

to participate in the trial during antenatal visits. The patient information leaflets and consent forms were handed out to consenting patients, and signed.

Immediately after the patients were put under general anaesthesia, 21-gauge preheparinised intravenous cannula was inserted in the antecubital veins for blood collections. Blood samples were collected at time 0 in a 5 mls plain tube as base line. After the baby and placenta were delivered, 225mg (30mls volume) of ropivacaine was injected/sprinkled into the wound. Five mls sprinkled into the visceral peritoneum, 5 mls into the parietal peritoneum, 10 mls into and above the rectus sheath and 10mls subcutaneously under the skin. The time of commencement of ropivacaine injection was noted. At 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 16 hours and 24 hours post caesarean section, blood was drawn for plasma concentration of ropivacaine. The blood samples were centrifuged at a 4000 revolutions per minute using Biofuge Heraeus Centrifuge over 10 minutes at room temperature. The serum separated was stored at a temperature of -20 degree Celsius. The specimens were placed in a refrigerated storage facility within 60 minutes of drawing the blood. Serum concentrations were determined using reversed high-performance liquid chromatography, by a 2005 described method.[1] A 500 micro litre of the plasma sample was placed in a 10 mls siliconised tube. 100 micro litre of internal standard made of bupivacaine and 250 micro litre of 0.1M of sodium hydroxide were added and mixed. To this mixture was added ethyl acetate used for extraction of the bupivacaine (internal standard) and ropivacaine. The mixture was centrifuged for 6 min at 1500g. The upper organic phase was removed to another tube and another 2ml of ethyl acetate added and centrifuged. Both organic phase samples were evaporated to obtain dry samples. The evaporation was carried out using a stream of nitrogen at a temperature of -40 degrees Celsius. The extract was mixed with mobile phase solvent (100 micro litre) and 25 micro litre aliquot forcibly injected into the HPLC machine at a flow rate of 0.8ml/min. The HPLC machine, Waters Separation 2690 model with a Photodiode array detector, consisted of a pump, an ultraviolet detector set to 215 nm and an integrator.

The mobile phase solvent was a mixture of acetonitrite, methanol and a buffer of phosphate adjusted to a pH of 4.0

3.3. Results

In one patient, the baseline sample at time 0, showed presence of ropivacaine. This was assumed to be due to incorrect labelling of the samples. The samples from the patient were omitted from analysis.

Data from the remaining nine women was analysed. Samples were not obtainable at all the time intervals. The mean parity (SD) of the women was 2.6 (1.5), age 35.4 (2.9) years, weight 79.67 (18.3) kg and mean height was 162.4 (5.0) cm. There was no patient who weighed less than 65kg. The maximum serum concentration (Cmax) of ropivacaine following administration of 225mg via this route was 1553 (SD 793) ug/L obtained at 30 minutes following administration (Tmax). The concentration fell gradually over 24 hours. The missing data was responsible for variations in n. On several instances, patients in the trial declined taking blood samples while sleeping, especially at night or in the early hours of morning.

Table 3.1 Mean concentration of ropivacaine (µg/L) over time

Time (minutes)	0	15	30	60	120	240	480	960	1920
No. of participants	9	9	9	8	9	7	7	7	6
Mean (ug/ml)	0	1357	1553	1300	1030	980	707	645	582
Standard deviation	0	751	793	350	429	231	528	351	690

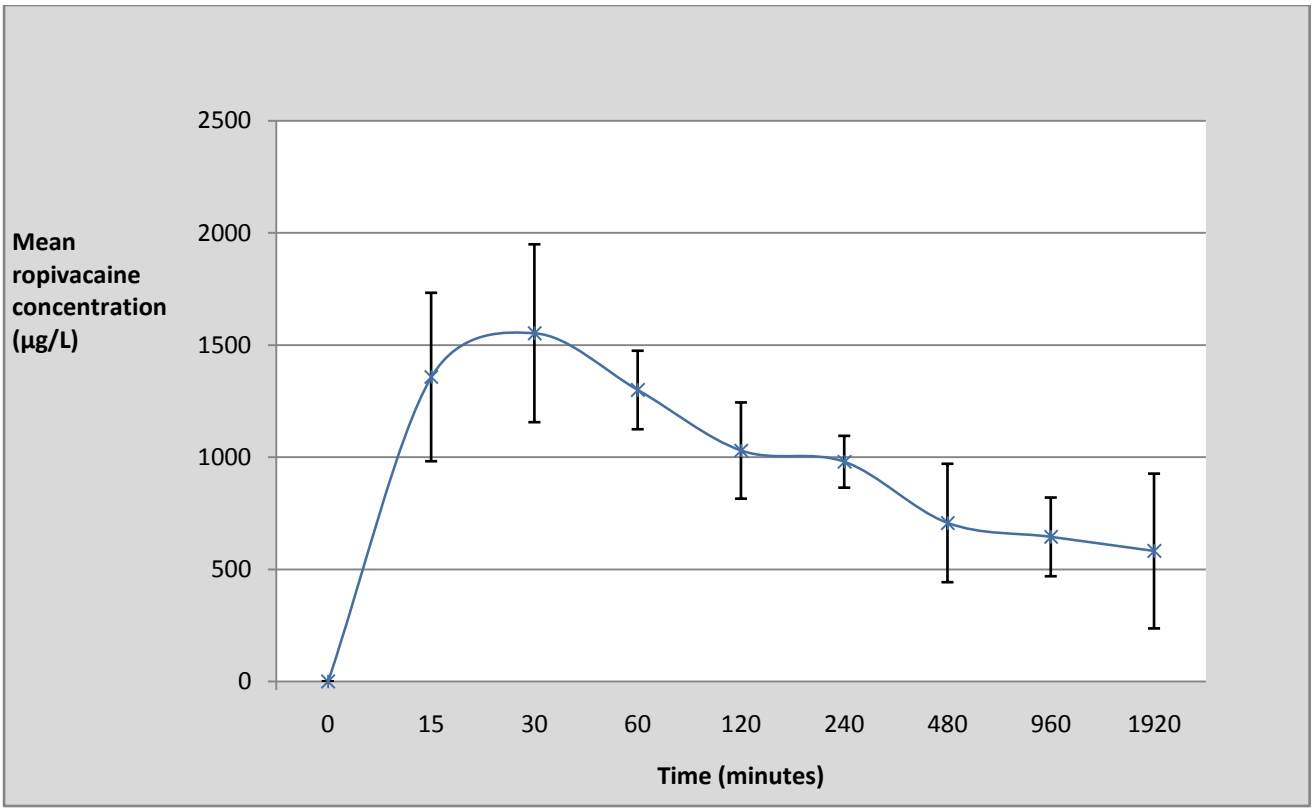

Figure 3.1 Mean concentration of ropivacaine (ug/ml) versus time (minutes).

3.4. Discussion

A pharmacokinetic study of plasma levels following intraperitoneal instillation of ropivacaine in combination with abdominal wall infiltration at caesarean section has not, according to the author's knowledge, previously been performed. The maximum plasma concentration (Cmax) reached within 30 minutes of drug administration, implies the rapid absorption of ropivacaine following this route of drug administration. This rapid absorption is postulated to be due to peritoneal administration of the local anaesthetic agent and exposure of the agent to open blood vessels breached during surgery.

Following brachial plexus block after a dose of 300mg ropivacaine, the Tmax (SD) was 54(22) minutes with a Cmax (SD)of 2300 (800) µg/L [2] The Cmax of ropivacaine(1553+-793 µg/L) in this study fell between levels reached after 72 hours of continuous epidural infusion after a cumulative dose of 2075+-206mg (2800+/-SD 500µg/L), and following 7.5mg/ml ropivacaine epidural block for caesarean delivery at 1100 (200) µg/L. [1] The toxic serum level of ropivacaine is not well characterised but the safety margin is between 1000 – 3000 µg/L, even though levels as high as 5000 µg/L has been reached without adverse effect. [3] The study limitation was the missing data due to patients who declined giving blood samples while sleeping at night. The results indicated that the dose used would be safe to use and even for those having caesarean delivery under local anaesthetic infiltration only.

The number of patients who participated in this study was too small to establish if there is any correlation between the individual patient's weight and the maximum serum concentration.

3.5. Conclusion

The maximum concentration of ropivacaine using a dosage of 225mg by infiltration through all layers of the anterior abdominal wall incision, including spraying of peritoneum at caesarean section, was 1553 (SD) 793 µg/L /L. This is well below levels reached following brachial plexus block and 72 hours of continuous epidural infusion. This level falls within the safety range in humans.

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CHAPTER FOUR

LOCAL ANAESTHETIC WOUND INFILTRATION AND ABDOMINAL NERVES BLOCK DURING CAESAREAN SECTION FOR POSTOPERATIVE PAIN RELIEF – A SYSTEMATIC REVIEW

Synopsis

This chapter of the thesis dealt with a summarised analysis of all suitable trials, including the clinical trial above, in a systematic review, to advise health care providers on the role of adjuvant local anaesthetic infiltration in post-caesarean section analgesia. This review was done and published under the Pregnancy and Childbirth group of the Cochrane collaboration, United Kingdom and followed the guidelines of Cochrane systematic review. Twenty trials involving 1150 patients were analysed, it was concluded that local anaesthetic wound infiltration and abdominal nerve blocks as adjuncts to regional and general anaesthesia, were of benefit in caesarean section pain relief by reducing opioid consumption. Non-steroidal anti-inflammatory drugs as an adjuvant conferred additional pain relief. The format of this chapter, including tables and referencing, follows the Cochrane conventions. This explains some of the disparity in presentation of this chapter as compared to previous ones. The systematic review has generated considerable interest in both scientific and in the lay press worldwide. This may change clinical practice and contribute to the advancement of medical knowledge.

Abstract

Caesarean section delivery is becoming more frequent. Childbirth is an emotion-filled event and the mother needs to bond with her newborn baby as early as possible. Any intervention that leads to improvement in pain relief is worthy of investigation. Local anesthetics, either on their own or in combination with opioids or non-steroidal anti-inflammatory drugs, have been employed as an adjunct to other post-operative pain relief strategies. Conflicting reports were noted.

Objectives

To assess the effects of local anesthetic agent wound infiltration/irrigation and/or abdominal nerve blocks on post caesarean section pain, and the mother's well being and interaction with her baby.

Search methods

The Cochrane Pregnancy and Childbirth Group's Trials Register was searched (April 2009).

Selection criteria

Randomised controlled trials of pre-emptive local analgesia during caesarean section.

Data collection and analysis

The student extracted data. One of the supervisors checked the data (GJH). The data published by the author, was checked for eligibility by an independent Cochrane reviewer.

Results

Twenty studies (1150 patients) were included. Patients, who had a caesarean section performed under regional analgesia and had wound infiltration, showed a decrease in morphine consumption at 24 hours (SMD -1.70mg; 95% confidence interval (CI) -2.75 to -0.94) compared to placebo.

In patients under general anesthesia, with caesarean section wound infiltration and peritoneal spraying with local anesthetic (one study, 100 participants), the need for opioid rescue was reduced (risk ratio (RR) 0.51; 95% CI 0.38 to 0.69). The numerical pain score (0 to10) within the first hour was also reduced (mean difference (MD) -1.46; 95% CI -2.60 to -0.32).

Patients with regional analgesia, who had local anesthetic and non-steroidal anti-inflammatory cocktail wound infiltration, consumed less morphine (one study, 60 participants; MD -7.40 mg; 95% CI -9.58 to -5.22) compared to local anesthetic control.

Patients who had regional analgesia with abdominal nerves blocked, had decreased opioid consumption (four studies, 175 participants; MD -25.80 mg; 95% CI -50.39 to -5.37).

For the outcome of visual analogue scale 0 to 10 over 24 hours, no advantage was demonstrated in the single study of fifty participants who had their wounds infiltrated with a mixture of local analgesia and narcotics versus local analgesia. Addition of ketamine to the local analgesia in patients who had regional analgesia does not confer any advantage.

Authors' conclusions

Local anaesthetics infiltration, including the peritoneum and abdominal nerve blocks as adjuncts to regional or general anaesthesia, are of benefit in caesarean sections, by reducing opioid consumption. Non-steroidal anti-inflammatory drugs as an adjuvant may confer additional pain relief.

Plain language summary

Childbirth by operation (caesarean section) is becoming more frequent. Caesarean section requires an anaesthesia (pain blocking interventions) - either spinal, spinal epidural, epidural block (pain blocking by injection in the spine) or general anaesthesia (making the patient to sleep without feeling the pain).

Post-operative pain is managed with a combination of an opioid such as morphine or pethidine and other analgesics. Such opioids cause sedation and they can be transferred to breast milk, also sedating the newborn infant. Childbirth is a deeply emotional experience and involves bonding with the newborn and starting breastfeeding. Improvements in pain relief that make the post delivery period more comfortable for the mother are important. During the operation, local anaesthetics can be injected to block the nerves before cutting the skin or after closing the skin at the end of the operation (abdominal nerve block), or the wound can be irrigated or infiltrated with anaesthetic solution to reduce pain after operation (pre-emptive wound analgesia).

Twenty trials, that were of predetermined adequate qualities and involving 1150 patients, were identified. These trials were carried out in both developed and developing countries. In general, local anaesthesia wound infiltration was of benefit in patients having a caesarean section requiring regional anaesthetics, because of a reduction in

the use of opioid analgesia. Patients undergoing general anaesthesia, who had wound infiltration with local anaesthetics and down to the surface of the wound, required lower amounts of opioids in the first 24 hours post-operation compared to saline control. Those patients who had a general anaesthetic and the abdominal wall nerves blocked had reduced pain scores within the first 24 hours post-operative.

Patients who had regional anaesthesia and abdominal nerves blocked, also benefited by decrease in opioid requirements. Non-steroidal anti-inflammatory drugs (another form of pain relieving medication) provided additional pain relief but with more side effects of generalised body itching. The commonly used local anaesthetic agents do have side effects - but these are very rare - ranging from allergy to blood vessels, heart and nervous side effects. There was no report of side effects in infants following local anaesthetic infiltration, but the number of patients studied was small. The longer theatre time and cost of the local anaesthetic may be offset by less use of pain relieving medications after operation. The effect on the development of chronic pelvic pain should be an important area of research in the nearest future.

Background

Caesarean section delivery is becoming more frequent and is one of the most common major operative procedures performed worldwide. Widely varying rates of caesarean sections have been quoted from around the world. What is certain is that the rate is increasing. In the United States, a caesarean section rate of 26% for all births is reported (CDC 2002). It approaches 25% in Canada and is over 20% in England, Wales and Northern Ireland (RCOG 2001). In the private health sector in South Africa, one study noted a much higher figure of 57% (Tshibangu, 2002).

Childbirth is a profound emotional experience for a woman and her family. The mother needs to bond with the newborn baby as early as possible. The need for early breastfeeding cannot be over-emphasised. Breastfeeding is economical, and it is emotionally satisfying to most women. It helps to contract the uterus and accelerates the

process of uterine involution in the postpartum period. It promotes mother-infant bonding. It may also protect the breast against future cancer (Pernoll, 1991). Any form of intervention that leads to improvement in pain relief can positively impact on early breastfeeding. Prompt and adequate post-operative pain relief is therefore an important component of caesarean delivery that can make the immediate post-delivery period less discomforting and more emotionally gratifying. Management of post-operative pain after a caesarean section has mostly involved the use of opioids in combination with other forms of analgesics (multimodal analgesic regimen). Any intervention that can alleviate post-operative pain is worthy of investigation, and any procedural intervention that is performed while carrying out the surgery needs to be adequately assessed before being widely accepted as the norm.

Caesarean section is done under spinal anaesthesia, spinal epidural, epidural block or general anaesthesia. Intra-operatively, short- or medium-acting sedatives, narcotics and local anaesthesia have been employed as an adjunct to anaesthesia or to alleviate post-operative pain. Local anesthetics cause reversible blockade of impulse propagation along the nerve fibers by preventing the influx of sodium ions through the cell membrane of the nerve fibers. Several studies have given reports on pre-emptive local anesthetics (local anesthetic given during operation to prevent or reduce pain after operation) to relieve post-operative pain, ranging from being beneficial (Ganta, 1994; Johansson, 1997) to no benefit (Adams, 1991; Friedman, 2001).

The timing of local anesthetic administration may either be by pre- or post-incision abdominal nerve block - local anesthetics injected to block the nerves before cutting the skin at the beginning of operation, or after closing the skin at the end of operation (Trotter, 1991) - or pre- or post-incision abdominal wound infiltration (Ganta, 1994; Kumar, 1999). It may also be by continuous wound irrigation (Givens, 2002).

Several local anesthetic agents have been used as pre-emptive analgesia (xylocaine, bupivacaine or ropivacaine at different concentrations), either on their own, or in combination with opioids. The commonly used local anesthetic agents have side effects, even though very rare, ranging from allergy to cardiovascular and central nervous system effects. The effects on wound healing may be beneficial as the local anesthetic agent is often

combined with vasoconstrictors. Ropivacaine on its own has an intrinsic vasoconstricting property. Local anesthetics eventually get absorbed systemically and secreted in breast milk but side effects on breastfed babies have not yet been documented. This is in sharp contrast to morphine or pethidine, both of which have a significant transfer to breast milk and may have a sedative effect on the baby (Pernoll, 1991).

It is also important to consider the additional cost implication of this intervention. Should it prove to be of benefit, the actual cost of the local anesthetic and the added time needed to carry out the procedure may be justified, considering the long-term sequel of pain and immobility in the immediate post-caesarean section period.

Objectives

To assess the effects of local anesthetic agent wound infiltration/irrigation and/or abdominal nerve blocks on post-caesarean section pain relief; to assess the effect on the mother's physical, social and mental well being; and to assess the effect on the mother's ability to meet the physical, psychological and nutritional needs of the baby.

Methods

Criteria for considering studies for this review:

Types of studies

Prospective randomised controlled trials.

Types of participants

Women undergoing caesarean section, either electively or as an emergency.

Types of interventions

1. Local anesthetic agent wound infiltration versus placebo/no infiltration
2. Ilioinguinal/iliohypogastric nerve block versus placebo/no treatment
3. Local anesthetic agent versus other methods of pain relief

4. Comparison of different local anesthetic agent techniques

Types of outcome measures

1. Post-operative pain scores
2. Post-operative analgesia requirement
3. Time to first rescue analgesia
4. Post-operative fever
5. Duration of caesarean section
6. Onset of mobilisation
7. Onset of breastfeeding
8. Duration of any breastfeeding
9. Duration of exclusive breastfeeding
10. Minor side effects of the local anesthetic
11. Major side effects, e.g. central nervous system or cardiovascular
12. Duration of hospital stay
13. Post-operative wound infection
14. Women's pain relief satisfaction
15. Overall satisfaction
16. Occurrence of postnatal depression or neurotic/psychotic disorders
17. Chronic pelvic pain
18. Caregiver satisfaction
19. Cost

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-coordinator (April 2009). The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-coordinator and contains trials identified from:

1. Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. Weekly searches of MEDLINE;
3. Hand searches of 30 journals and the proceedings of major conferences;
4. Weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of hand searched journals and conference proceedings, and the list of journals reviewed via the current awareness service, can be found in the 'Specialised Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-coordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

We assessed for inclusion, all potential studies we identified as a result of the search strategy.

Data extraction and management

We designed a form to extract data. One review author extracted the data (Student-AAB) using the agreed form and the second author (supervisor GJH) cross-checked. No major discrepancies were identified. An independent

Cochrane reviewer assess for inclusion, the trial published by the Student. Details are in the appendix section. We used the Review Manager software (RevMan 2008) to double enter all the data.

Assessment of methodological quality of included studies

We assessed the validity of each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins, 2008). We described methods used for generation of the randomisation sequence for each trial.

(1) Sequence generation (checking for possible selection bias)

We have described for each individual study the method used to generate allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We have assessed the method as:

- Adequate (any truly random process, e.g., random number table; computer random number generator);
- Inadequate (any non-random process, e.g., odd or even date of birth; hospital or clinic record number)
- Unclear.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence in sufficient detail and determined whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as:

- Adequate (e.g., telephone or central randomization; consecutively numbered sealed opaque envelopes);
- Inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- Unclear.

(3) Blinding (checking for possible performance bias)

We have described for each included study the methods used, if any, to blind study participants and personnel, from knowledge of which intervention a participant received. We have judged studies to be at low risk of bias if

they were blinded, or if we judged that the lack of blinding could not have affected the results. We have assessed blinding separately for different outcomes or classes of outcomes. We have assessed the methods as:

- Adequate, inadequate, or unclear for participants;
- Adequate, inadequate, or unclear for personnel;
- Adequate, inadequate, or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We have described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We assessed methods as:

- Adequate;
- Inadequate;
- Unclear.

(5) Selective reporting bias

We have assessed the methods as:

- Adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- Inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- Unclear.

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan, 2008). We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar. When heterogeneity was found, we used random-effects analysis.

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Dealing with missing data

We analysed data on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

Assessment of heterogeneity

We applied tests of heterogeneity between trials, if appropriate, using the I^2 statistic. In the event of significant heterogeneity, we used a random-effects meta-analysis as an overall summary if we determined that this was appropriate.

Subgroup analyses

We performed sub-group analysis for patients who had general anaesthesia versus regional analgesia.

Sensitivity analyses

We excluded studies of poor quality (those rating B, C or D) in order to assess for any substantive difference to the overall result.

Results

Description of studies

We identified 40 studies. Twenty studies, involving 1150 patients, carried out in both developed and developing countries spanning almost two decades, met the inclusion criteria - *see* Characteristics of included studies table for details of the individual studies. For details of the 12 excluded studies, *see* Characteristics of excluded studies. There are four ongoing studies (Carvel, 2007; Griffiths, 2005; Holmstrom, 2006; Wolfson, 2007) and four studies are awaiting classification (Bensghir, 2008; Kanchanakitsakul, 1999; Kuppuvelumani, 1992; Rackelboom, 2008).

Risk of bias in included studies

See the results of the assessment of trial quality.

Effects of interventions

1. Wound infiltration with local anesthetics only versus control

Patients who had caesarean sections performed under regional anaesthesia and had wound infiltration had a decrease in morphine consumption at 24 hours (three studies, 126 participants; standardised mean difference (SMD) -1.70mg; 95% confidence interval (CI) -2.75, -0.94) compared to placebo. There was no difference in visual analogue pain.

In one study of patients under general anesthetic, who had the caesarean section wound infiltrated and peritoneal spraying with local anesthetic (one study, 100 participants), the need for opioid rescue was reduced (risk ratio (RR) 0.51; 95% CI 0.38 to 0.69). Numerical pain score (0 to 10) within the first hour was reduced (MD -1.46; 95% CI -2.60 to -0.32).

The amount of oral Tramadol/acetaminophen (375 mg paracetamol + 150 mg tramadol) consumed was reduced in the local anesthetic group compared to saline control (MD -2.35 mg; 95% CI -3.62 to -1.08).

2. Local anesthetics versus local anesthetic and non-steroidal anti-inflammatory drugs (NSAID) mixture

Patients operated under regional anaesthesia and who had a local anesthetic and NSAID cocktail wound infiltration consumed less morphine in the first 18 hours (one study, 60 participants; MD -7.40 mg; 95% CI -9.58 to -5.22) compared to local anesthetic only control. There was no difference in the occurrence of vomiting or reduction in antiemetic usage (RR 1.40 mg; 95% CI 0.90 to 2.16).

3. Anterior abdominal nerves block with local anesthetic versus control

Patients who had regional anaesthesia and had the abdominal nerves blocked had decreased opioid consumption (four studies, 175 participants; MD -25.80 mg; 95% CI -50.39 to -5.37) but no difference in visual analogue pain score (0 to 10) (one study, 59 participants; RR -5.00; 95% CI -11.27 to -1.21).

4. Local anesthetics versus local anesthetics + narcotics

No advantage, in the visual analogue scale over 24 hours, was demonstrated in the single study of 50 participants who had wound infiltration with a mixture of local anesthetic and narcotics versus local anesthetics.

5. Local anesthetics versus local anesthetics + ketamine

Addition of ketamine to the local anaesthetic in patients, who had regional anaesthesia, does not confer any advantage neither in terms of narcotic consumption nor patient satisfaction. (One study and fifty participants).

Discussion

Minimising pain after caesarean section is best achieved using a multimodal approach. Local anesthetics from lidocaine to the more recent ropivacaine have been used as pre-emptive analgesics since the 1980s. Clinical trials were only published in the early 1990s. Local anesthetics has been used with patients undergoing general anesthetic, regional anaesthesia and rarely purely under local anesthetic when other anaesthesia was unavailable

or unsafe. Various routes of administration have been tested such as subcutaneous wound infiltration, infiltration through all layers of the abdomen, continuous wound instillation or iliohypogastric/ilioinguinal nerve blocks. Ultrasound guided nerve blocks may soon be explored. Local anesthetic has been used either alone or in combination with non-steroidal anti-inflammatory agents or ketamine.

This review showed that patients undergoing regional analgesia who had local anesthetic infiltration or abdominal nerve block had reduction in the use of post-operative opioids. Addition of non-steroidal anti-inflammatory drugs to the local anesthetic for caesarean section wound infiltration conferred additional advantage. This may be explained because of the addition of another type of analgesic with a different mode of action. Opioid consumption may not be the optimal method of pain assessment because of being influenced by the patients' fear of dependency, but this effect is balanced by the randomisation process. Significant results must be regarded with caution because of testing at multiple times and the results are mostly based on single trials involving few patients.

None of the trials addressed the effect on chronic pelvic pain and cost implications.

Authors' conclusions

Implications for practice

In general, local anaesthesia is of benefit in patients having a caesarean section by reduction in opioid consumption. It can be recommended, with consideration to affordability, as part of the multimodal approach to pain relief.

Implications for research

A cost-benefit analysis is needed. There will be more theatre time spent and cost of the local anesthetic and accessories. This may be offset by less use of post-operative analgesia. A pharmacokinetic study of local anesthetic absorption following wound and peritoneal infiltration is necessary. Ultrasound guided direct block of

the anterior abdominal wall nerves during caesarean sections should be explored. An important research agenda will also be the effect of the intervention on chronic pelvic pain.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), and the Group's Statistical Adviser. An independent Cochrane reviewer (Theresa Lawrie) assessed the author's published work for inclusion eligibility in the systematic review.

Declaration of interest

A.A. Bamigboye has conducted a study of ropivacaine wound infiltration and peritoneal spray for caesarean section pain relief as part of a degree program, supervised by G.J. Hofmeyr. The study was included in this review after assessment by an independent Cochrane Reviewer for eligibility.

Characteristics of studies

Characteristics of included studies

Bamigboye 2008

Methods	Randomised double-blind, placebo-controlled trial.
Participants	100 consented patients undergoing elective caesarean section.
Interventions	50 patients received 225 mg ropivacaine if 64 kg or more and 3 mg/kg if less. The control received equivalent volume of saline. All layers of the anterior abdominal incision were infiltrated including the peritoneum. Postoperatively, the women had pethidine, diclofenac injection and Tramadol/acetaminophen.
Outcomes	Need for rescue pethidine within one hour of caesarean section and occurrence of severe pain at the end of the first hour. Other outcomes were numerical pain rating scores, amount of other analgesics consumed and side effects such as nausea, vomiting and pruritus.
Notes	An independent reviewer, T Lawrie, assessed the trial and was judged to be eligible.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	No	Computer-generated random sequence.
Allocation concealment?	Yes	Adequate by drawing ropivacaine or saline from a

		galipot prepared by theatre nursing manager.
Blinding?	Yes	Sealed envelope, surgeon, anesthetist, midwife blinded to allocation
Incomplete outcome data addressed?	Yes	Few outcomes omitted especially at night when patients requested not to be disturbed. It balanced out in both arms of allocation.
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No known bias recognised.

Bell 2002

Methods	Randomised double-blind placebo-controlled trial.
Participants	59 patients for caesarean section randomised to receive nerve block or saline placebo.
Interventions	31 patients had ilioinguinal-iliohypogastric nerve block with 0.5% bupivacaine with adrenaline and 28 had saline placebo.
Outcomes	Post-operative morphine use and visual analogue pain scores.
Notes	

Risk of bias table

Item	Judgment	Description

Adequate sequence generation?	Yes	Computer-generated block randomisation.
Allocation concealment?	Yes	A - Adequate.
Blinding?	Yes	Double blinded
Incomplete outcome data addressed?	Yes	No incomplete data
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No recognised bias

Caulry 2003

Methods	Randomised placebo-controlled trial.
Participants	30 patients undergoing spinal anaesthesia randomised into 10 each of saline, ropivacaine and diclofenac.
Interventions	Wound irrigation in each group.
Outcomes	Visual analogue pain scores and use of morphine.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Generated random sequence, but not stated how this was achieved.

Allocation concealment?	Unclear	Not stated
Blinding?	Unclear	Not stated
Incomplete outcome data addressed?	Unclear	No evidence of incomplete outcome
Free of selective reporting?	Yes	No evidence of selective reporting
Free of other bias?	Yes	No noted bias

Chen 1990

Methods	Randomised clinical trial.
Participants	36 patients were randomised into 12 no treatment, 12 plain Marcaine and 12 Marcaine with adrenaline.
Interventions	Ilioinguinal nerve block after caesarean section.
Outcomes	Pain, times of pethidine injection, the first time and dosage of pethidine injection, postpartum hemorrhage and uterine atony.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Randomised trial but method of generation of allocation sequence unclear

Allocation concealment?	Unclear	Not stated
Blinding?	Unclear	Not stated
Incomplete outcome data addressed?	Yes	There were no drop outs
Free of selective reporting?	Yes	No selective reporting
Free of other bias?	Yes	Chinese Mandarin language translated by professionals.

Ganta 1994

Methods	Randomised single-blind placebo-controlled trial.
Participants	62 patients having elective caesarean section under general anaesthesia.
Interventions	21 patients had bilateral ilioinguinal nerve block with 0.5% bupivacaine, 20 patients had wound infiltration with 0.5% bupivacaine and 21 received no local anaesthetic.
Outcomes	Visual analogue scale pain scores in first 24 hours and mean morphine consumption in 24 hours.
Notes	

Risk of bias table

Item	Judgment	Description

Adequate sequence generation?	Unclear	Method of generation not stated.
Allocation concealment?	No	Not concealed
Blinding?	No	Not blinded
Incomplete outcome data addressed?	Yes	Data complete
Free of selective reporting?	Yes	No selective reporting
Free of other bias?	Yes	Free

Givens 2002

Methods	Randomised double-blind placebo-controlled trial.
Participants	36 patients for planned caesarean section.
Interventions	20 patients with wound irrigation with 0.25% bupivacaine versus 16 women with normal saline solution irrigation.
Outcomes	Post-operative morphine use and visual analogue pain scores.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Computer-generated randomisation schedule.
Allocation concealment?	Yes	Sealed packets that contained group assignments.

Blinding?	Yes	Adequately blinded to surgeons, patients and data recorder.
Incomplete outcome data addressed?	Yes	Complete outcome data.
Free of selective reporting?	Yes	No evidence of selective reporting.
Free of other bias?	Yes	No evidence of other bias.

Kumar 1999

Methods	Randomised-controlled trial.
Participants	50 ASA I and II patients for elective caesarean section.
Interventions	24 patients received pre-incisional 40 ml of 0.5% bupivacaine versus 26 who received 40 ml of bupivacaine and 2 mg morphine mixture.
Outcomes	Visual analogue pain scores at different hours in the first 24 hours and side effects of vomiting, nausea and pruritus.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Randomised trial but method of generation of sequence not stated.
Allocation concealment?	Unclear	Method of concealment not stated.

Blinding?	Unclear	Trial stated to be blinded.
Incomplete outcome data addressed?	Yes	Outcome data was complete.
Free of selective reporting?	Yes	No selective reporting noted.
Free of other bias?	Yes	No other bias noted.

Kuppuvelamini 1992

Methods	Randomised controlled trial.
Participants	60 patients undergoing caesarean section under general anaesthesia.
Interventions	A mixture of 0.5% bupivacaine with adrenaline with 1% xylocaine was injected to block the ilioinguinal/iliohypogastric in 30 patients versus control in another 30 patients who did not receive abdominal nerve block.
Outcomes	Time to breastfeeding, total pethidine requirement over 24 hours and duration of action of the block.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Random sequence but method of generation not stated.

Allocation concealment?	Unclear	No concealment.
Blinding?	No	Control arm did not receive placebo or control block.
Incomplete outcome data addressed?	Yes	Data was complete.
Free of selective reporting?	Yes	No evidence of selective reporting.
Free of other bias?	Yes	No other bias noted.

Lacrosse 2004

Methods	Prospective randomised trial.
Participants	55 healthy parturients for caesarean section under spinal anaesthesia.
Interventions	19 patients had wound irrigation with 300mg of diclofenac for 48hrs, 18 patients had ropivacaine 0.2% and 18 women had saline control.
Outcomes	Local ropivacaine wound infiltration is superior to diclofenac only in the first 24 hours but diclofenac has a better opioid sparing effect.
Notes	Lacrosse 2004 looked at delayed benefit of diclofenac for residual pain at 1-6 months.

Risk of bias table

Item	Judgment	Description

Adequate sequence generation?	Unclear	Random allocation but method of generation not stated.
Allocation concealment?	Unclear	Not stated.
Blinding?	Unclear	Not stated.
Incomplete outcome data addressed?	Yes	Data complete.
Free of selective reporting?	Yes	No selective reporting noted.
Free of other bias?	Yes	Free of bias.

Lavand'homme 2007

Methods	Randomised double-blind placebo-controlled trial.
Participants	90 patients randomly allocated to receive saline, diclofenac or 0.2% ropivacaine. 30 in each group.
Interventions	Continuous wound infiltration of the allocated interventions.
Outcomes	Post-operative morphine consumption, parietal and visceral visual analogue pain scores.
Notes	

Risk of bias table

Item	Judgment	Description

Adequate sequence generation?	Yes	Computer-generated random sequence.
Allocation concealment?	Yes	Adequate.
Blinding?	Yes	Adequate; the patient, the peri-operative management team and the data collectors were all blinded.
Incomplete outcome data addressed?	Yes	Data was complete.
Free of selective reporting?	Yes	No selective reporting.
Free of other bias?	Yes	Free of other bias.

Marbaix 2004

Methods	Randomised prospective trial.
Participants	55 healthy parturients for elective caesarean section under spinal anaesthesia.
Interventions	19 patients had wound irrigation with 300 mg of diclofenac for 48 hours, 18 patients had ropivacaine 0.2%, 18 women had saline control.
Outcomes	Visual analogue pain scores and morphine consumption.
Notes	Continuation of the same trial presented authored by Lacrosse 2004.

Risk of bias table

Item	Judgment	Description

Adequate sequence generation?	Unclear	Unstated.
Allocation concealment?	Unclear	Unstated.
Blinding?	Unclear	Unstated.
Incomplete outcome data addressed?	Yes	Complete data.
Free of selective reporting?	Yes	Free.
Free of other bias?	Yes	Free.

McDonnell 2008

Methods	Randomised controlled trial.
Participants	50 patients undergoing caesarean sections under spinal anaesthesia.
Interventions	1.5 mg/kg ropivacaine, per side injection into the transversus abdominis plane (TAP) versus saline TAP block.
Outcomes	Morphine requirement, prolonged and superior analgesia up to 36 hours postoperative.
Notes	TAP block targets sensory innervations of anterior abdominal wall before leaving the triangle of Petit.

Risk of bias table

Item	Judgment	Description

Adequate sequence generation?	Yes	Random number table.
Allocation concealment?	Yes	Opaque sealed envelopes.
Blinding?	Yes	Patients, anesthesiologists, surgeon and postoperative team were all blinded.
Incomplete outcome data addressed?	Yes	Complete.
Free of selective reporting?	Yes	Free.
Free of other bias?	Yes	Free of bias.

Mecklem 1995

Methods	Randomised double-blind placebo-controlled trial.
Participants	79 patients undergoing caesarean section under spinal analgesia.
Interventions	Patients were allocated to receive either saline or 0.25% bupivacaine.
Outcomes	Visual analogue pain scores, morphine consumption and gastrointestinal side effect.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Tables of random numbers.

Allocation concealment?	Yes	Adequate by using coded ampoules of bupivacaine and saline.
Blinding?	Yes	Coded ampoules of saline or Marcaine.
Incomplete outcome data addressed?	Yes	Complete outcome data.
Free of selective reporting?	Yes	Free.
Free of other bias?	Yes	No other bias.

Pavy 1994

Methods	Randomised trial.
Participants	40 patients for elective caesarean section.
Interventions	Group A - 20 patients received 0.5% bupivacaine, group B - 20 patients received saline.
Outcomes	Pain scores, pruritus and nausea.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Random table was used.
Allocation concealment?	Yes	Adequate.

Blinding?	Yes	To all parties.
Incomplete outcome data addressed?	Yes	Complete data.
Free of selective reporting?	Yes	Free.
Free of other bias?	Yes	Free of other bias.

Pirbudak 2004

Methods	Randomised double blind.
Participants	60 patients undergoing caesarean delivery under spinal anaesthesia.
Interventions	Group 1 received 40 ml of 0.25% bupivacaine + 100 mg tramadol + 20 mg tenoxicam. Group 2 received normal saline.
Outcomes	Reduction in post-operative analgesic use and prolongation of analgesic requirement time.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Randomised trial but method of randomisation not stated.
Allocation concealment?	Unclear	Not described.

Blinding?	Unclear	Method of achieving blinding not described.
Incomplete outcome data addressed?	Yes	Data complete.
Free of selective reporting?	Yes	No evidence of selective reporting.
Free of other bias?	Yes	Free of other bias.

Rosaeg 1997

Methods	Randomised controlled trial.
Participants	40 patients for elective caesarean sections under spinal analgesia.
Interventions	Group 1: experimental patients received intrathecal morphine, incisional bupivacaine and ibuprofen and acetaminophen. Group 2 received intravenous morphine weaned to acetaminophen and codeine. Both groups received 7.5mg/ml solution bupivacaine spinal analgesia.
Outcomes	Visual analogue pain scores at rest and at mobilisation. Time to first walking, eating, bowel movement and voiding.
Notes	

Risk of bias table

Item	Judgment	Description

Adequate sequence generation?	Yes	Computer-generated set of random numbers.
Allocation concealment?	Yes	Adequate concealment.
Blinding?	Yes	Blinded.
Incomplete outcome data addressed?	Yes	Data complete.
Free of selective reporting?	Yes	No evidence of selective reporting.
Free of other bias?	Yes	Free.

Solak 1999

Methods	Randomised trial.
Participants	30 ASA patients for elective caesarean sections.
Interventions	Patients randomised to receive either 20 ml of 0.5%bupivacaine or saline.
Outcomes	Visual analogue pain scale scores, analgesic requirement and cortisol level.
Notes	No formal interpretation from Turkish available.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Randomised trial, method unknown.

Allocation concealment?	Yes	Concealed.
Blinding?	Yes	Blinded.
Incomplete outcome data addressed?	Yes	Data complete.
Free of selective reporting?	Yes	No selective reporting.
Free of other bias?	No	Language barrier.

Trotter 1991

Methods	Randomised double-blind trial.
Participants	28 patients for elective caesarean section.
Interventions	Group B received 0.5% bupivacaine and the control group C received saline.
Outcomes	Morphine consumption, pain scores, sedation level and nausea.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Random sequence, method of generation unknown.
Allocation concealment?	Yes	Adequately concealed.
Blinding?	Yes	Solutions supplied in numbered vials.

Incomplete outcome data addressed?	Yes	Complete.
Free of selective reporting?	Yes	Free.
Free of other bias?	Yes	Free of any other bias.

Zohar 2002

Methods	Prospective randomised double-blind study that assessed the analgesic efficacy of ketamine when administered as an adjuvant to bupivacaine for patient controlled wound instillation following caesarean section.
Participants	50 term parturients undergoing caesarean section under spinal anaesthesia.
Interventions	A multi-holed device is placed in the wound and connected to a patient controlled pump. Group 1 had bupivacaine and Group 2 combined with ketamine.
Outcomes	Visual analogue scale for pain, rescue morphine, patient satisfaction.
Notes	

Risk of bias table

Item	Judgment	Description

Adequate sequence generation?	Unclear	Method of randomisation not stated.
Allocation concealment?	Unclear	Method not stated
Blinding?	Unclear	Double blinded trial even though how it was achieved was not described.
Incomplete outcome data addressed?	Yes	Complete.
Free of selective reporting?	Yes	Free.
Free of other bias?	Yes	Free.

Zohar 2006

Methods	Prospective, randomised, double-blind, placebo-controlled trial.
Participants	90 parturients (ASA1 & 2) undergoing elective caesarean section.
Interventions	Group 1: 30 patients had wound instillation via a patient-controlled analgesic infusion pump of 0.25% bupivacaine and 75 mg intravenous diclofenac. Group 2 received only bupivacaine instillation. Group 3 received only diclofenac infusion. 30 patients in each group.
Outcomes	Rescue analgesic required, visual analogue pain scale, nausea and patient satisfaction.
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Computer-generated randomisation schedule.
Allocation concealment?	Yes	Adequate.
Blinding?	Yes	Adequately blinded.
Incomplete outcome data addressed?	Yes	Data complete.
Free of selective reporting?	Yes	Free.
Free of other bias?	Yes	Free.

Characteristics of excluded studies

Bisson 1991

Reason for exclusion	Inadequate published data. Only pre-entry characteristics of the study populations were given. No table or data of outcome was depicted or tabulated. The conclusion of the study is that of no significant difference in the visual pain rating scale and the amount of analgesic requirement in patients who had bupivacaine wound infiltration under general anaesthesia versus placebo.

Bunting 1988

Reason for exclusion	Inadequate data to include in the meta-analysis. However, the study showed longer time to require rescue analgesic and reduce pain scores in the nerve block group. There was no side effect noted in both groups.

Christie 1993

Reason for exclusion	Inadequate data to include in the meta-analysis and hyperalgesia as an outcome measure was not part of the original protocol for this review.

Farrugia 1995

Reason for exclusion	Inadequate data to include in the meta-analysis. However, the study showed that patients who had nerve block required less rescue opioids compared to wound infiltration.

Foster 1983

Reason for exclusion	No randomisation, consecutive patients were allocated. Inadequate data for analysis.

Huffnagle 1996

Reason for exclusion	Inadequate data to include in the meta-analysis. However, the study

	showed that women who had pre-incision abdominal nerve block had better pain control.

Lipscomb 2002

Reason for exclusion	Inadequate data for inclusion into the meta-analysis. However, the study demonstrated that continuous infusion of 0.25% bupivacaine into caesarean section wound reduces postoperative narcotic use.

Momani 2001

Reason for exclusion	Data not adequate for statistical analysis. However, the outcome of trial of bupivacaine 0.25% caesarean section wound infiltration showed reduction in postoperative analgesic requirement.

Raffo 1999

Reason for exclusion	Inadequate data to include in the meta-analysis. However, the study showed that pre-incision local anaesthesia infiltration does not improve post-operative analgesia in women who underwent spinal/epidural.

Ranta 2004

Reason for exclusion	Inadequate data to include in the meta-analysis. However, the study

	showed that local wound irrigation for pain relief was comparable in efficacy to epidural analgesia.

Schultz 2001

Reason for exclusion	Inadequate data excludes this study.

Thiry 2006

Reason for exclusion	A randomised trial of parietal infiltration of ropivacaine versus saline control. No information on data but trial concluded reduction in postoperative narcotic usage.

Characteristics of ongoing studies

Carvalho 2007

Study name	Efficacy of transversus abdominis plane block for post caesarean delivery analgesia.
Methods	Randomised trial.
Participants	Women for caesarean delivery.
Interventions	Patients will be assigned to receive 0.375% ropivacaine TAP block or a placebo.
Outcomes	Pain scores, opioid consumption.

Starting date	December 2007.
Contact information	jose.carvalho@uhn.on.ca
Notes	Study is still recruiting.

Griffiths 2005

Study name	A prospective comparison of early postoperative analgesia in caesarean section using bilateral ilio-inguinal block and subcutaneous morphine.
Methods	Randomised double-blind, parallel assignment, efficacy trial.
Participants	100 women for caesarean section.
Interventions	5% bupivacaine.
Outcomes	Decreased postoperative pain and narcotic use. Time to first analgesia.
Starting date	01/02/06.
Contact information	Dr J Griffiths, box 2002, Ivanhoe east, VIC Australia.
Notes	

Holmstrom 2006

Study name	Caesarean delivery and post-operative pain management with local anaesthesia.
Methods	Randomised double-blind, parallel assignment, efficacy trial.
Participants	100 pregnant women with scheduled caesarean delivery.
Interventions	5% bupivacaine with epinephrine versus control.
Outcomes	Decreased postoperative pain and narcotic use.
Starting date	February 2006.
Contact information	Aron Deutch abdmstrom@hotmail.com
Notes	

Wolfson 2007

Study name	A randomised double-blind, placebo controlled trial of ilioinguinal iliohypogastric nerve blocks and neuraxial morphine for post caesarean analgesia.
Methods	No details yet.
Participants	Women presenting for non-emergency caesarean section.
Interventions	IIIH block in one group versus saline.
Outcomes	Trial is ongoing.
Starting date	Unknown.
Contact information	
Notes	

References to studies

Included studies

Bamigboye 2008

Bamigboye AA. & Hofmeyr GJ. Ropivacaine wound infiltration and peritoneal spray for post caesarean section pain relief. *International Journal of Gynecology & Obstetrics* 2008; 102(2):160-4.

Bell 2002

Bell EA, Jones BP, Olufolabi AJ, Dexter F, Phillips-Bute B, Greengrass RA, et al. Iliohypogastric-ilioinguinal peripheral nerve block for post-cesarean delivery analgesia decreases morphine use but not opioid-related side effects. *Canadian Journal of Anesthesia* 2002; 49(7):694-700.

Caulry 2003

Caulry C, Roelants F, Waterloos H, Yamgnane A, Lavand'homme P. Continuous wound irrigation with ropivacaine or diclofenac for postoperative analgesia after cesarean section. *Regional Anesthesia and Pain Medicine* 2003; 28(5 Suppl 1):49.

Chen 1990

Chen C, Seah YS, Ng YT, Chuah EC, Tan PP. Ilioinguinal nerve blockade with or without epinephrine for analgesia after caesarean section. *Acta Anaesthesiologica Taiwanica* 1990; 28:351-5.

Ganta 1994

Ganta R, Samra SK, Maddineni VR, Furness G. Comparison of the effectiveness of bilateral ilioinguinal nerve block and wound infiltration for postoperative analgesia after caesarean section. *British Journal of Anaesthesia* 1994; 72:229-30.

Givens 2002

Givens VA, Lipscomb GH, Meyr N.L. A randomised trial of postoperative wound irrigation with local anesthetic for pain after cesarean delivery. *American Journal of Obstetrics and Gynecology* 2002; 186:1188-91.

Kumar 1999

Kumar Das A, Wig J, Dhaliwal L. Preincisional local infiltration of bupivacaine and a mixture of bupivacaine and morphine for pain following lower segment cesarean section (a comparative evaluation). *Journal of Anaesthesiology and Clinical Pharmacology* 1999; 15:317-20.

Kuppuvelamini 1992

Kuppuvelumani P, Jaradi H, Delilkan A. Abdominal nerve blockade for postoperative analgesia after caesarean section. *Asia-Oceania Journal of Obstetrics and Gynaecology* 1993; 19(2):165-9.

Lacrosse 2004

Lacrosse D, Roelants F, Mercier V, Waterloos H, Lavand'homme P. Continuous wound irrigation with ropivacaine or diclofenac after cesarean: immediate and delayed benefits. *International Journal of Obstetric Anesthesia* 2004; 13(3): S20.

Lavand'homme 2007

Lavand'homme PM, Roelants F, Waterloos H, De Kock MF. Postoperative analgesic effects of continuous wound infiltration with diclofenac after elective cesarean delivery. *Anesthesiology* 2007;106(6): 1220-5.

Marbaix 2004

Marbaix C., Roelants F., Mercier V., Waterloos H., Lacrosse D. & Lavand'homme P. Post caesarean section analgesia with continuous local infusion of ropivacaine or diclofenac. *International Journal of Obstetric Anesthesia* 2004; 13(3):S19.

McDonnell 2008

McDonnell JG, Curley G, Carney J, Benton A, Costello J, Maharaj CH, et al. The analgesic efficacy of transversus abdominis plane block after cesarean delivery: a randomised trial. *Anesthesia & Analgesia* 2008; 106(1):186-91.

Mecklem 1995

Mecklem DW, Humphrey MD, Hicks RW. Efficacy of bupivacaine delivered by wound catheter for post-caesarean section analgesia. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1995; 35(4):416-21.

Pavy 1994

Pavy T.J.G., Gambling D.R., Kliffer A.P., Munro A., Merrick P.M. & Douglas MJ. Effect of pre-operative skin infiltration with 0.5% bupivacaine on postoperative pain following cesarean section under spinal anesthesia. *International Journal of Obstetric Anesthesia* 1994; 3:199-202.

Pirbudak 2004

Pirbudak L, Balat O, Karadasli H, Ugur MG, Oner U. Single perioperative wound infiltration with combination of bupivacaine, tramadol, and tenoxicam for pain relief after cesarean delivery with spinal anesthesia. *Pain Clinic* 2004;16(3):287-91.

Pirbudak L. Single perioperative wound infiltration with combination of bupivacaine, tramadol and tenoxicam for pain relief after cesarean delivery with spinal anesthesia. *Regional Anesthesia and Pain Medicine* 2003; 28(5 Suppl 1): 59.

Rosaeg 1997

Rosaeg O.P., Lui A.C., Cicutti N.J., Bragg P.R., Crossan M.L. & Krepski B. Peri-operative multimodal pain therapy for caesarean section: analgesia and fitness for discharge. *Canadian Journal of Anaesthesia* 1997; 44(8):803-9.

Solak 1999

Solak M., Yildirim S., Senel A.C. & Erciyes N. [The effects of preincisional bupivacaine infiltration on surgical stress response and postoperative analgesia in caesarean section]. *Turk Anesteziyoloji Ve Reanimasyon* 1999; 27:182-5.

Trotter 1991

Trotter T.N., Hayes-Gregson P., Robinson S., Cole L., Coley S. & Fell D. Wound infiltration of local anaesthetic after lower segment caesarean section. *Anaesthesia* 1991;46(5): 404-7.

Zohar 2002

Zohar E, Luban I, Zunser I, Shapiro A, Jedeikin R, Fredman B. Patient-controlled bupivacaine wound instillation following cesarean section: the lack of efficacy of adjuvant ketamine. *Journal of Clinical Anesthesia* 2002; 14:505-11.

Zohar 2006

Zohar E, Shapiro A, Eidinov A, Fishman A, Fredman B. Postcaesarean analgesia: the efficacy of bupivacaine wound instillation with and without supplemental diclofenac. *Journal of Clinical Anesthesia* 2006; 18(6):415-21.

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Bisson 1991

Bisson D, Cornes H, Bigrigg A. Does wound infiltration with bupivacaine improve post-operative pain relief following caesarean section? *Obstetrics and Gynaecology Today* 1991; 2:86-7.

Bunting 1988

Bunting P. & McConachie I. Ilioinguinal nerve blockade for analgesia after caesarean section. British Journal of Anaesthesia 1988; 61(6):773-5.

Christie 1993

Christie J.M. & Chen G.W. Secondary hyperanalgesia is not affected by wound infiltration with bupivacaine. *Canadian Journal of Anaesthesia* 1993; 40:1034-7.

Farrugia 1995

Farrugia M., Mamo J., Padovani A., Pace M. & Felice D. Bupivacaine local nerve block vs wound edge infiltration after caesarean section with spinal anaesthesia. *27th British Congress of Obstetrics and Gynaecology,* Dublin, Ireland July 4-7; 1995:509.

Foster 1983

Foster W.H., Mjekevu T., Olsen G., Orlikowski C. & Larsen J.V. Low spinal anaesthesia combined with local anaesthesia for caesarean section - an evaluation. *South African Medical Journal* 1983; 63:17-20.

Huffnagle 1996

Huffnagle HJ, Leighton BL, Norris MC, Arkoosh BA. Ilioinguinal iliohypogastric nerve blocks - before or after cesarean section? *Anesthesiology* 1992; 77(3A):A980.

Huffnagle HJ, Norris MC, Leighton BL, Arkoosh VA. Ilioinguinal iliohypogastric nerve blocks- before or after cesarean delivery under spinal anesthesia? *Anesthesia & Analgesia* 1996; 82:8-12.

Lipscomb 2002

Lipscomb G.H. & Meyer N.L. A randomised trial of postoperative wound irrigation with local anesthetic for pain after cesarean delivery [abstract]. *Obstetrics & Gynecology* 2002; 99(4):8S.

Momani 2001

Momani O. Controlled trial of wound infiltration with bupivacaine for post operative pain relief after caesarean section. *Bahrain Medical Bulletin* 2001; 23(2):84-6.

Raffo 1999

Raffo A.M., Wold S.M., Asrat T., Rumney P.J. & Walker C.K. Pre-emptive analgesia using local anesthesia for women undergoing cesarean section. *American Journal of Obstetrics and Gynecology* 1999;180 (1 Pt 2):S94.

Ranta 2004

Ranta P, Kukkonen J, Rawal N, Ohtonen P, Raudakoski T, Ala-Kokko T. The analgesic efficacy of regional levobupivacaine compared to epidural analgesia after caesarean delivery. *International Journal of Obstetric Anesthesia* 2004; 13(3):S17.

Schultz 2001

Schultz JR, Bell EA, Muir HA, Phillips-Bute B, Reynolds JD. Iliohypogastric-ilioinguinal (ihii) nerve blocks may offer no benefit as an adjunct to neuraxial morphine for post cesearean section (cs) analgesia [abstract]. *Anesthesiology* 2001; 94(1A):A99.

Thiry 2006

Thiry J.C., Cres J.C., Janssens N. & Joris J. How to improve analgesia after caesarean section: infiltration with ropivacaine [abstract]. *Regional Anesthesia and Pain Management* 2006; 31(5 Suppl 1):3.

Studies awaiting classification

Bensghir 2008

Bensghir M, Elwali A, Miller C, Azendour H, Drissi M, Bakkali H, et al. [Effects of skin infiltration with ropivacaine 0,75% on postoperative pain after caesarean section]. *Gynécologie, Obstétrique & Fertilité* 2008; 36(5):516-20.

Kanchanakitsakul 1999

Kanchanakitsakul P. The effectiveness of post-operative wound infiltration with bupivacaine for post-operative analgesia after cesarean section. *Thai Journal of Obstetrics and Gynaecology* 1999; 11(4):258.

Kuppuvelumani 1992

Kuppuvelumani P. Abdominal field block as post-operative analgesia for caesarean section under general anaesthesia. *Regional Anesthesia* 1992;17(3S):126.

Rackelboom 2008

Rackelboom TJ, Pasquier P, Goffinet F, Beaussier M, Mignon A. Analgesic infiltrations after cesarean section: which site of administration & cost effectiveness. *Anesthesiology* 2008; 109: A1121.

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Carvalho 2007

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Data and analyses of outcome

1. Wound infiltration with local anesthetic only versus control

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Total morphine consumption as defined by trial author in the first 24 hours	3	126	Std. Mean Difference (IV, Random, 95% CI)	-1.72 [-2.35, -1.09]
1.1.1 General anaesthesia	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
1.1.2 Regional anaesthesia	3	126	Std. Mean Difference (IV, Random, 95% CI)	-1.72 [-2.35, -1.09]
1.2 Total pethidine consumed 24 hours postdelivery	1	97	Mean Difference (IV, Fixed, 95% CI)	-44.00 [-108.31, 20.31]
1.2.1 General anaesthesia	1	97	Mean Difference (IV, Fixed, 95% CI)	-44.00 [-108.31, 20.31]
1.2.2 Regional	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Visual analogue scale (0-10) at 24 hours	2	56	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-1.72, 0.94]
1.3.1 Regional anaesthesia	2	56	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-1.72, 0.94]

1.3.2 General anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.4 Numerical pain score (0-10) at 1 hour	1	100	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-2.60, -0.32]
1.4.1 General anaesthesia	1	100	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-2.60, -0.32]
1.4.2 Regional anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.5 Numerical pain score (0-10) at 8 hours	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-3.29, 2.13]
1.5.1 General	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-3.29, 2.13]
1.5.2 Regional	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.6 Numerical pain score at 24 hours	1	97	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.67, 1.05]
1.6.1 General anaesthesia	1	97	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.67, 1.05]
1.6.2 Regional	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

1.7 Experience of severe pain 15 minutes after delivery	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.09, 0.42]
1.7.1 General anaesthesia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.09, 0.42]
1.7.2 Regional anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.8 Need for pethidine rescue within 1 hour of delivery	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.38, 0.69]
1.8.1 General anaesthesia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.38, 0.69]
1.8.2 Local anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.9 Experience of severe pain 2 hours post caesarean section delivery	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.11, 0.88]
1.9.1 General anaesthesia	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.11, 0.88]
1.9.2 Regional anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.10 Experience of severe pain 4 hours after caesarean delivery	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.28, 1.19]
1.10.1 General anaesthesia	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.28, 1.19]
1.10.2 Regional anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.11 Experience of severe pain (0-10) 8 hours after caesarean delivery	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.35, 1.45]

1.11.1 General anaesthesia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.35, 1.45]
1.11.2 Regional anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.12 Experience of severe pain 16 hours post caesarean delivery	1	96	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.11, 1.11]
1.12.1 General anaesthesia	1	96	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.11, 1.11]
1.12.2 Regional anaesthesia	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.13 Experience of severe pain 24 hours after caesarean delivery	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.27, 2.50]
1.13.1 General anaesthesia	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.27, 2.50]
1.13.2 Regional anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.14 Amount of rescue diclofenac (mg) used during hospitalisation	1	95	Mean Difference (IV, Fixed, 95% CI)	-43.79 [-66.95, -20.63]
1.14.1 General anaesthesia	1	95	Mean Difference (IV, Fixed, 95% CI)	-43.79 [-66.95, -20.63]
1.14.2 Regional anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.15 Amount of	1	95	Mean Difference (IV, Fixed, 95%	-2.35 [-3.62, -1.08]

tramadol/acetaminophen (375 mg paracetamol+150 tramadol) tablet used			CI)	
1.15.1 General anaesthesia	1	95	Mean Difference (IV, Fixed, 95% CI)	-2.35 [-3.62, -1.08]
1.15.2 Regional anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

2. Wound infiltration with local anesthetic + non-steroidal anti-inflammatory drugs versus control

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 No of attempts to activate PCA	1	60	Mean Difference (IV, Fixed, 95% CI)	-15.00 [-30.22, 0.22]
2.1.1 General anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.1.2 Regional anaesthesia	1	60	Mean Difference (IV, Fixed, 95% CI)	-15.00 [-30.22, 0.22]
2.2 Total morphine (mg) used in the first 18 hours	1	60	Mean Difference (IV, Fixed, 95% CI)	-7.40 [-9.58, -5.22]
2.2.1 General anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

2.2.2 Regional anaesthesia	1	60	Mean Difference (IV, Fixed, 95% CI)	-7.40 [-9.58, -5.22]
2.3 Need for antiemetic	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.17, 0.83]
2.3.1 General anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3.2 Regional anaesthesia	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.17, 0.83]
2.4 Patient satisfaction-good/excellent	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.02, 1.55]
2.4.1 General anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.4.2 Regional anaesthesia	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.02, 1.55]
2.5 Nausea	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.90, 2.16]
2.5.1 General anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.5.2 Regional anaesthesia	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.90, 2.16]
2.6 Pruritus	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.01, 3.23]
2.6.1 General anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.6.2 Regional anaesthesia	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.01, 3.23]

3. Abdominal nerve blocks with local anesthetic versus placebo block or no block

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Mean visual analogue scale	2	83	Mean Difference (IV, Fixed, 95%	-1.82 [-2.74, -0.90]

at 24 hours			CI)	
3.1.1 General anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.1.2 Regional anaesthesia	2	83	Mean Difference (IV, Fixed, 95% CI)	-1.82 [-2.74, -0.90]
3.2 Postoperative opioid use (mg) (as defined by trial authors)	4	175	Mean Difference (IV, Random, 95% CI)	-25.80 [-50.39, -1.21]
3.2.1 General anaesthesia	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.2.2 Regional anaesthesia	4	175	Mean Difference (IV, Random, 95% CI)	-25.80 [-50.39, -1.21]
3.3 No of times mother breast fed in 24 hours	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.61]
3.3.1 General anaesthesia	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.61]
3.3.2 Regional anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

4. Wound infiltration with local anesthetic versus local anesthetic + narcotics

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Mean visual analogue score at 2 hours	1	50	Mean Difference (IV, Fixed, 95% CI)	0.69 [-0.08, 1.46]

4.1.1 General anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.1.2 Regional anaesthesia	1	50	Mean Difference (IV, Fixed, 95% CI)	0.69 [-0.08, 1.46]
4.2 Mean visual analogue score at 12 hours	1	50	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.59, 0.95]
4.2.1 Regional anaesthesia	1	50	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.59, 0.95]
4.2.2 General anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.3 Mean visual analogue score at 24 hours	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.92, 0.62]
4.3.1 General anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.3.2 Regional anaesthesia	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.92, 0.62]

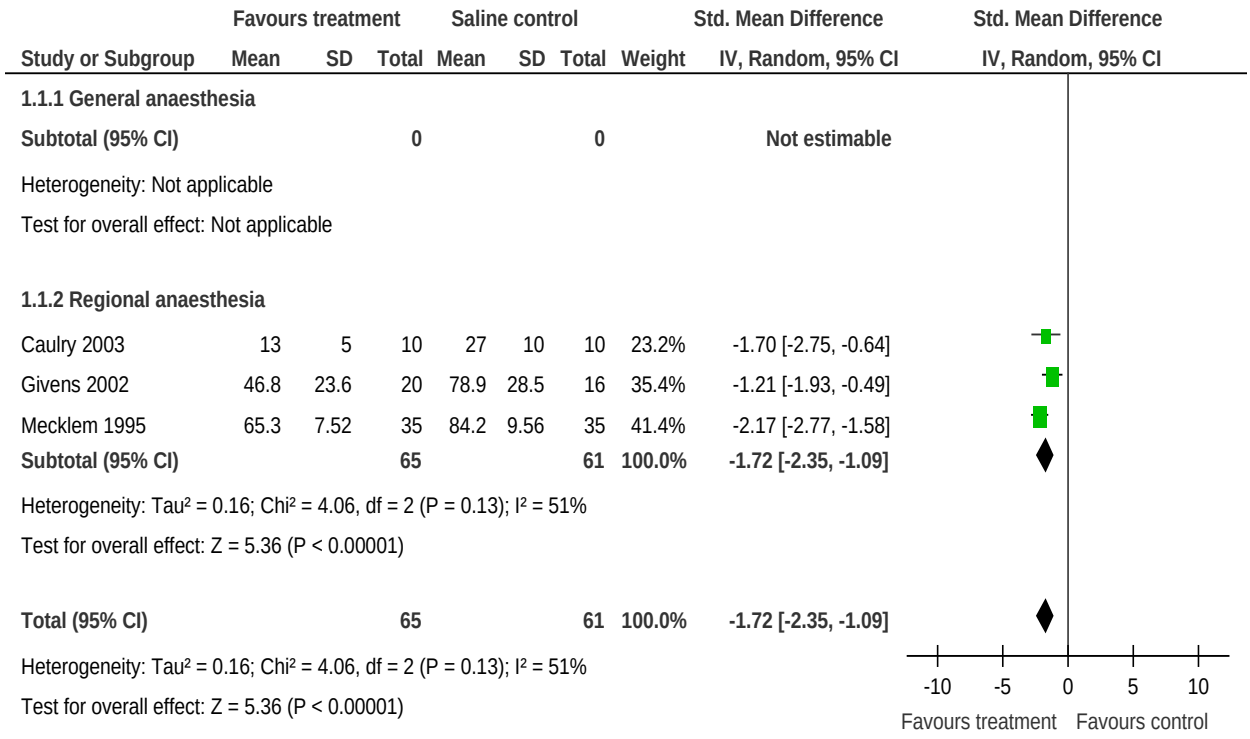
5. Wound infiltration with local anesthetic versus local anesthetic + ketamine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Total morphine consumed in	1	50	Mean Difference (IV, Fixed, 95%	0.10 [-2.74, 2.94]

the first 6 hours			CI)	
5.1.1 General anaesthesia	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.1.2 Regional anaesthesia	1	50	Mean Difference (IV, Fixed, 95% CI)	0.10 [-2.74, 2.94]
5.2 Patient satisfaction, good/excellent	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.42, 3.43]
5.2.1 General anaesthesia	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.42, 3.43]
5.2.2 Regional anaesthesia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Figures 1-17. Forest Plots of Comparisons

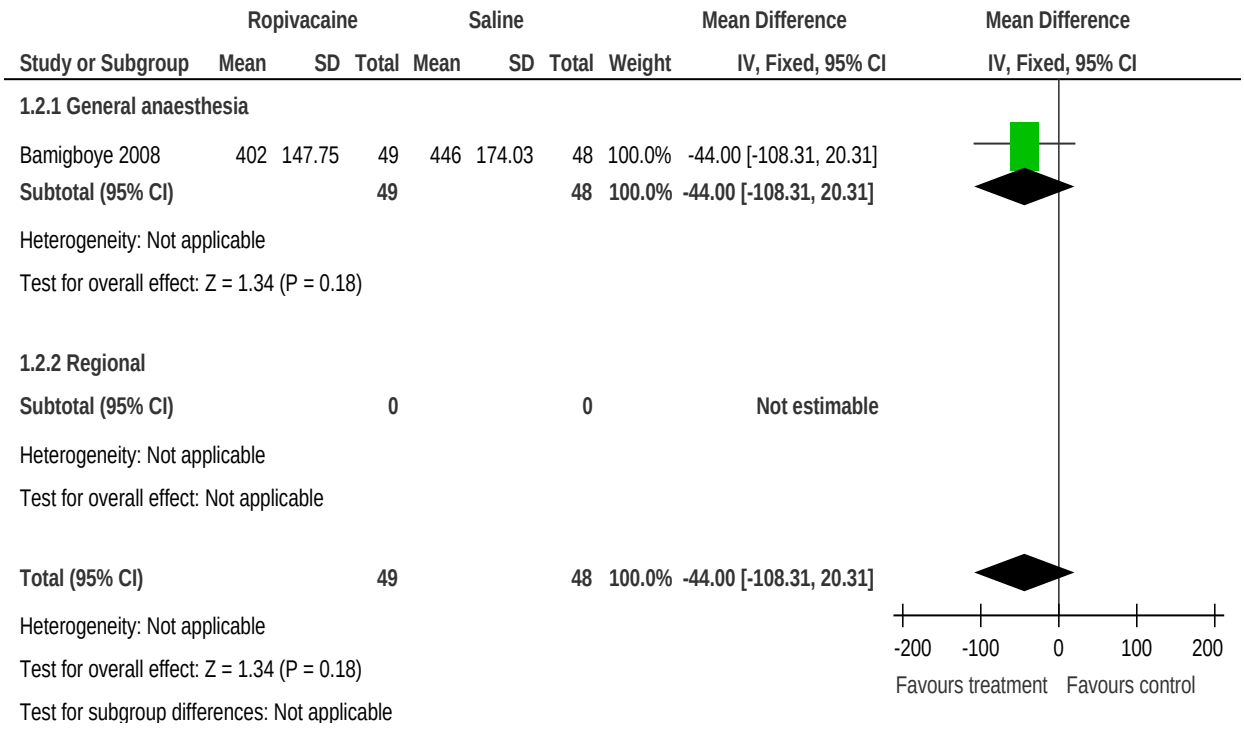
Figure 1 (Analysis 1.1)



Caption

Forest plot of comparison: 1 Wound infiltration with local anesthetic only versus control, outcome: 1.1 Total morphine consumption as defined by trial author in the first 24 hours.

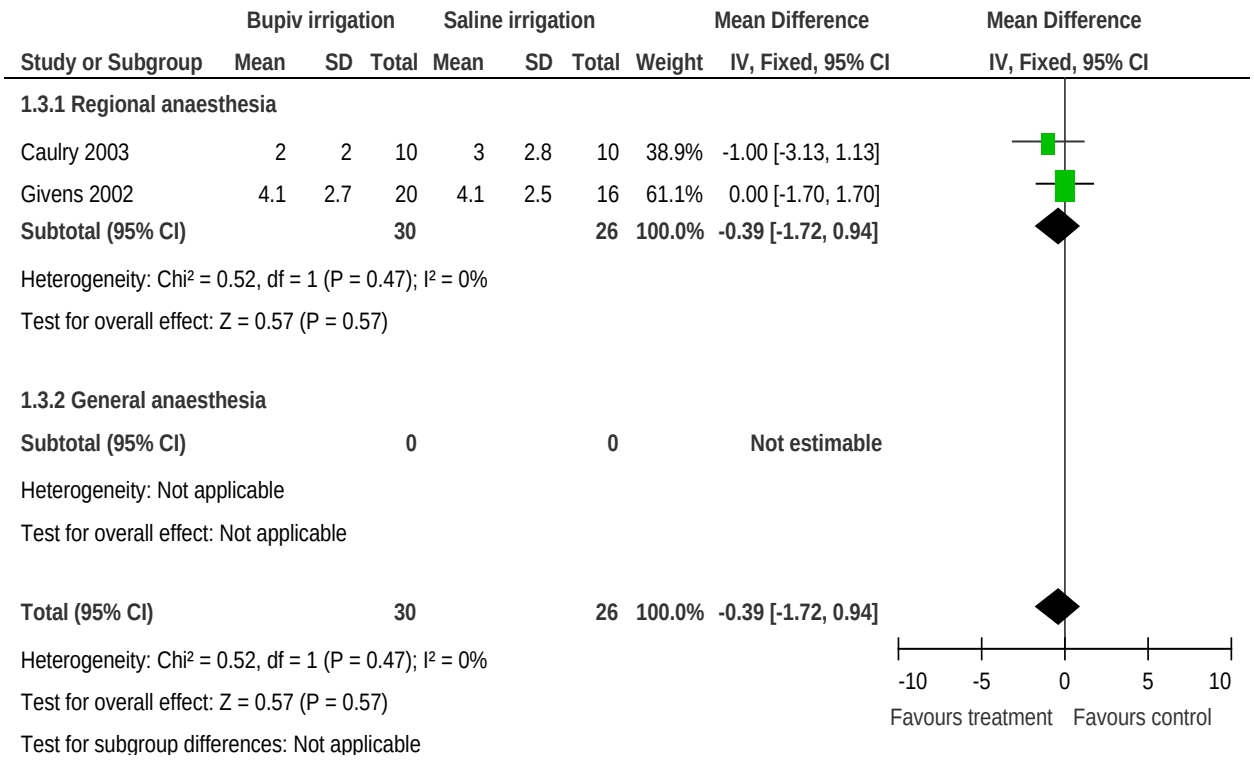
Figure 2 (Analysis 1.2)



Caption

Forest plot of comparison: 1 Wound infiltration with local anesthetic only versus control, outcome: 1.2 Total pethidine consumed 24 hours post delivery.

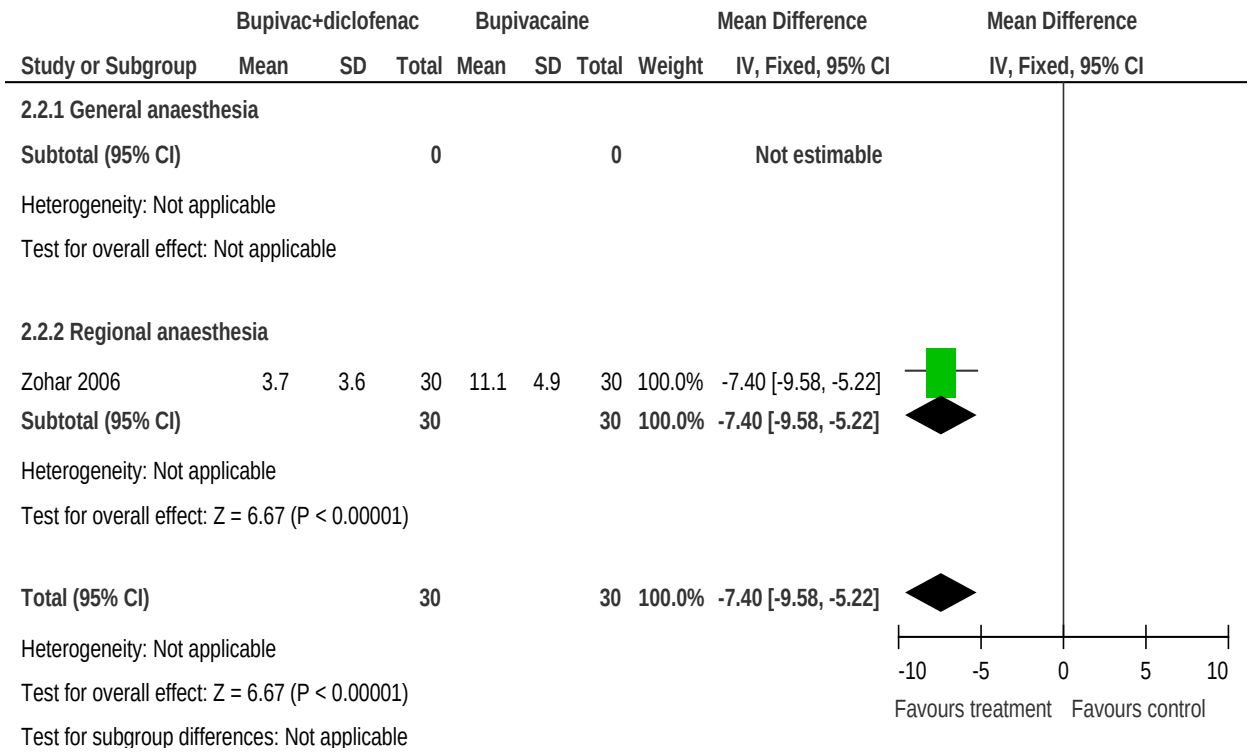
Figure 3 (Analysis 1.3)



Caption

Forest plot of comparison: 1 Wound infiltration with local anesthetic only versus control, outcome: 1.2 Visual analogue scale (0-10) at 24 hours.

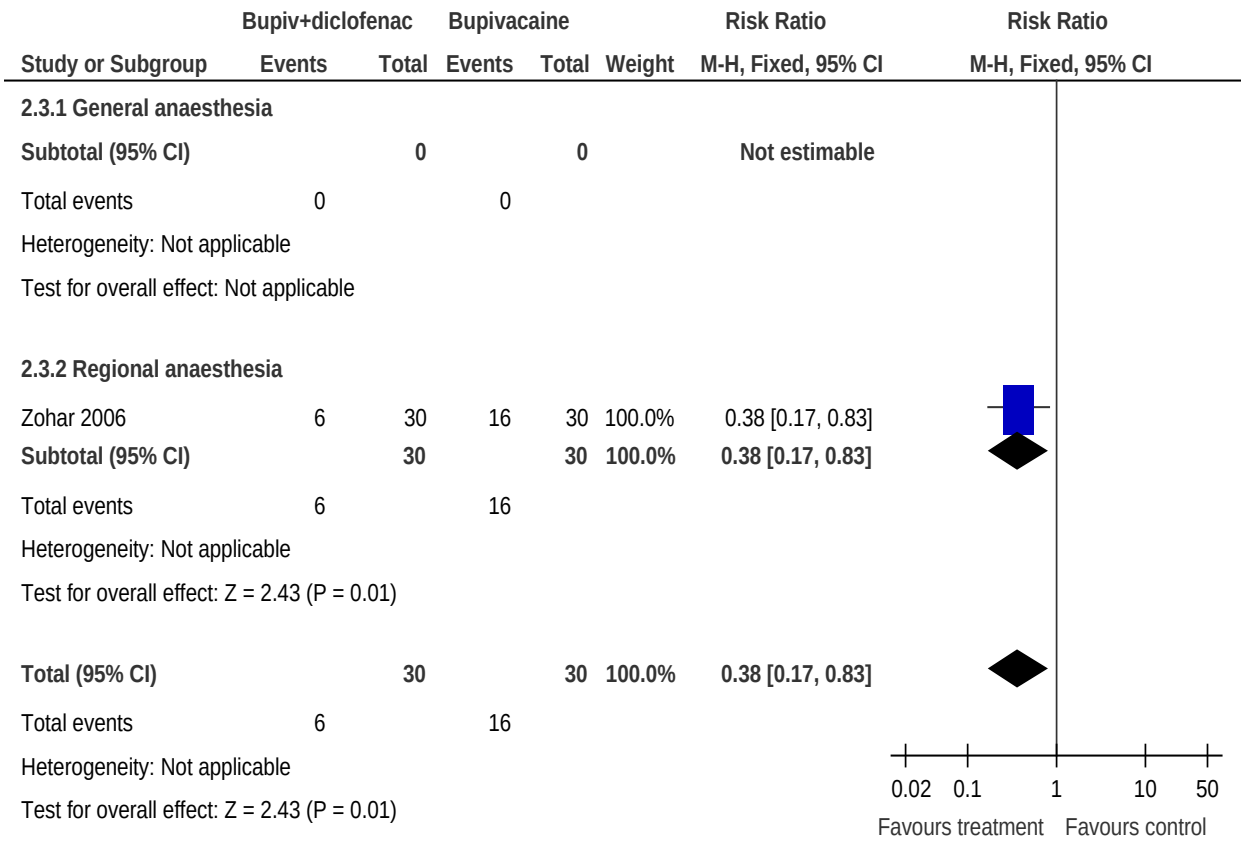
Figure 4 (Analysis 2.2)



Caption

Forest plot of comparison: 3. Wound infiltration with local anesthetic + non-steroidal anti-inflammatory drugs versus control, outcome: 3.2 Total morphine (mg) used in the first 18 hours.

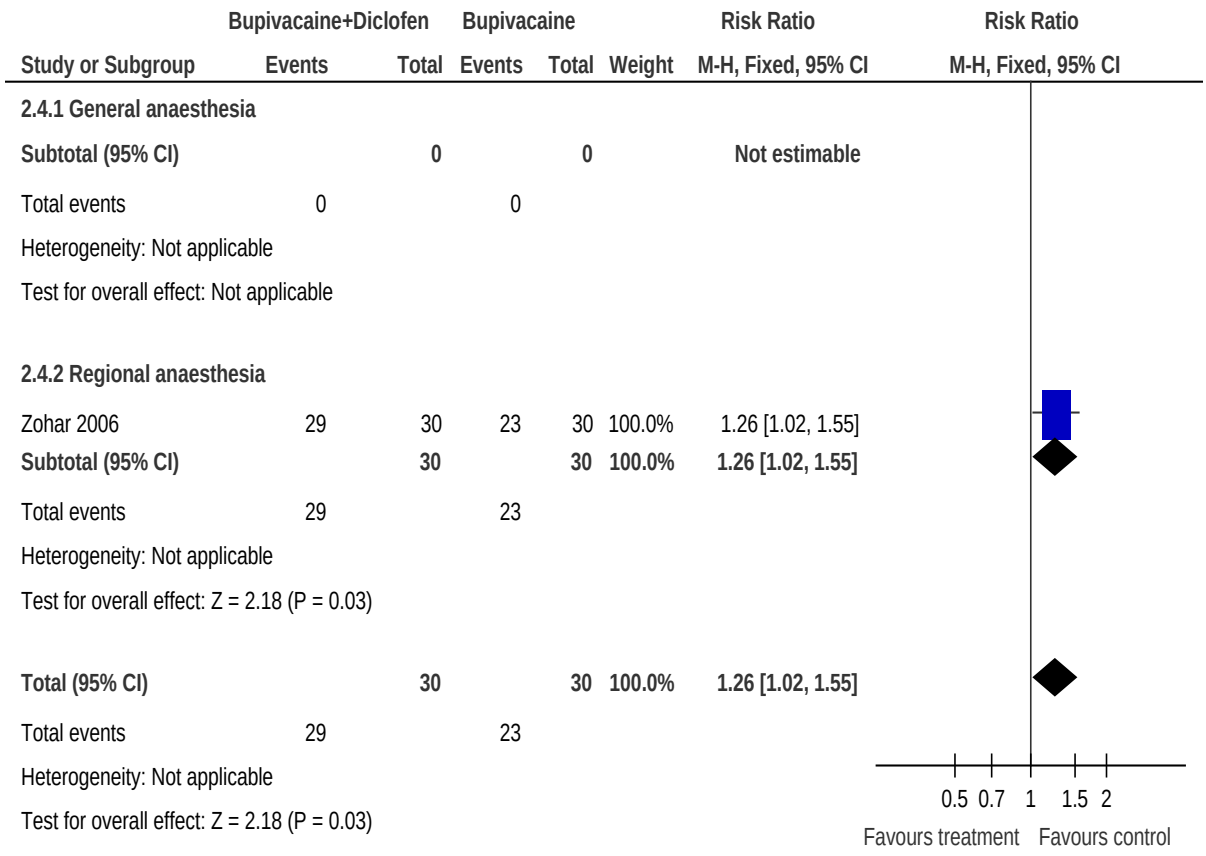
Figure 5 (Analysis 2.3)



Caption

Forest plot of comparison: 3 Wound infiltration with local anesthetic + non-steroidal anti-inflammatory drugs versus control, outcome: 3.3 Need for antiemetic.

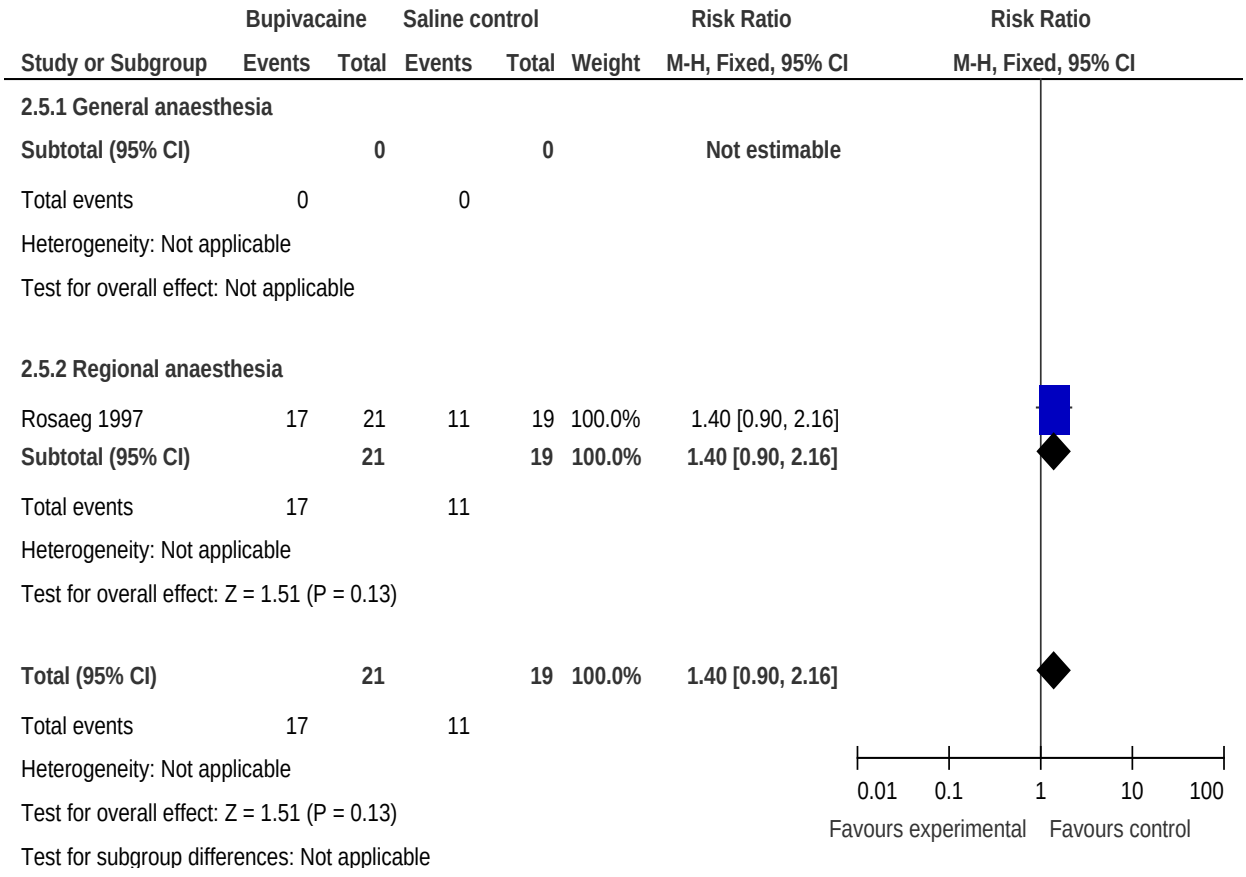
Figure 6 (Analysis 2.4)



Caption

Forest plot of comparison: 3 Wound infiltration with local anesthetic + non-steroidal anti-inflammatory drugs versus control, outcome: 3.4 Patient satisfaction-good/excellent.

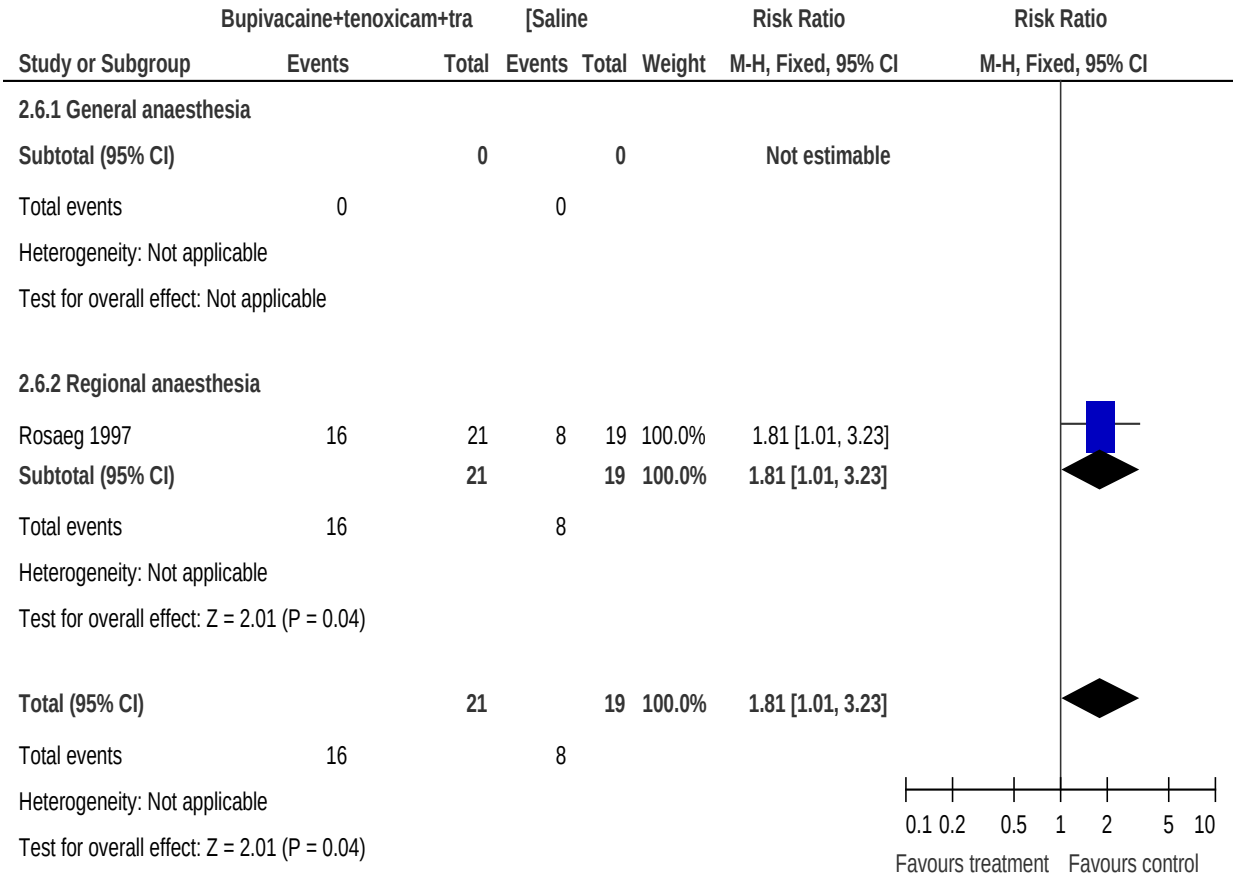
Figure 7 (Analysis 2.5)



Caption

Forest plot of comparison: 3 Wound infiltration with local anesthetic + non-steroidal anti-inflammatory drugs versus control, outcome: 3.5 Nausea.

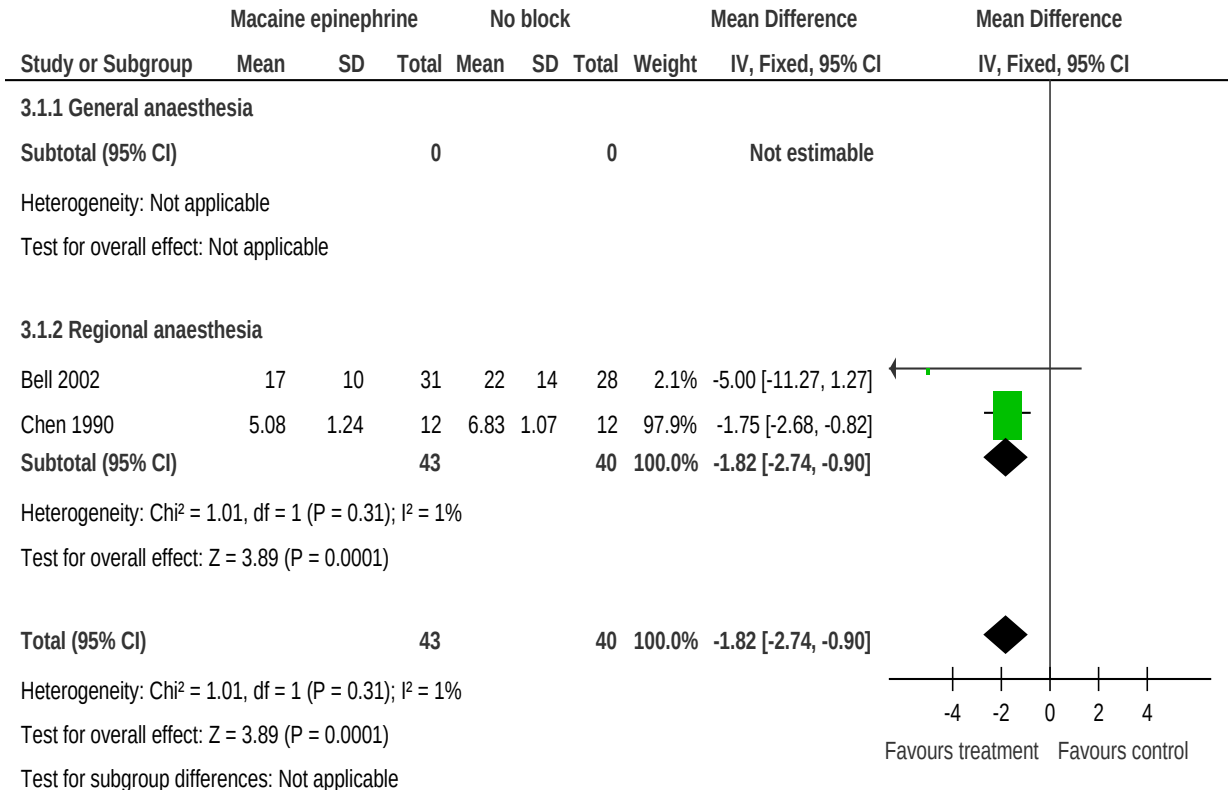
Figure 8 (Analysis 2.6)



Caption

Forest plot of comparison: 3 Wound infiltration with local anesthetic + non-steroidal anti-inflammatory drugs versus control, outcome: 3.6 Pruritus.

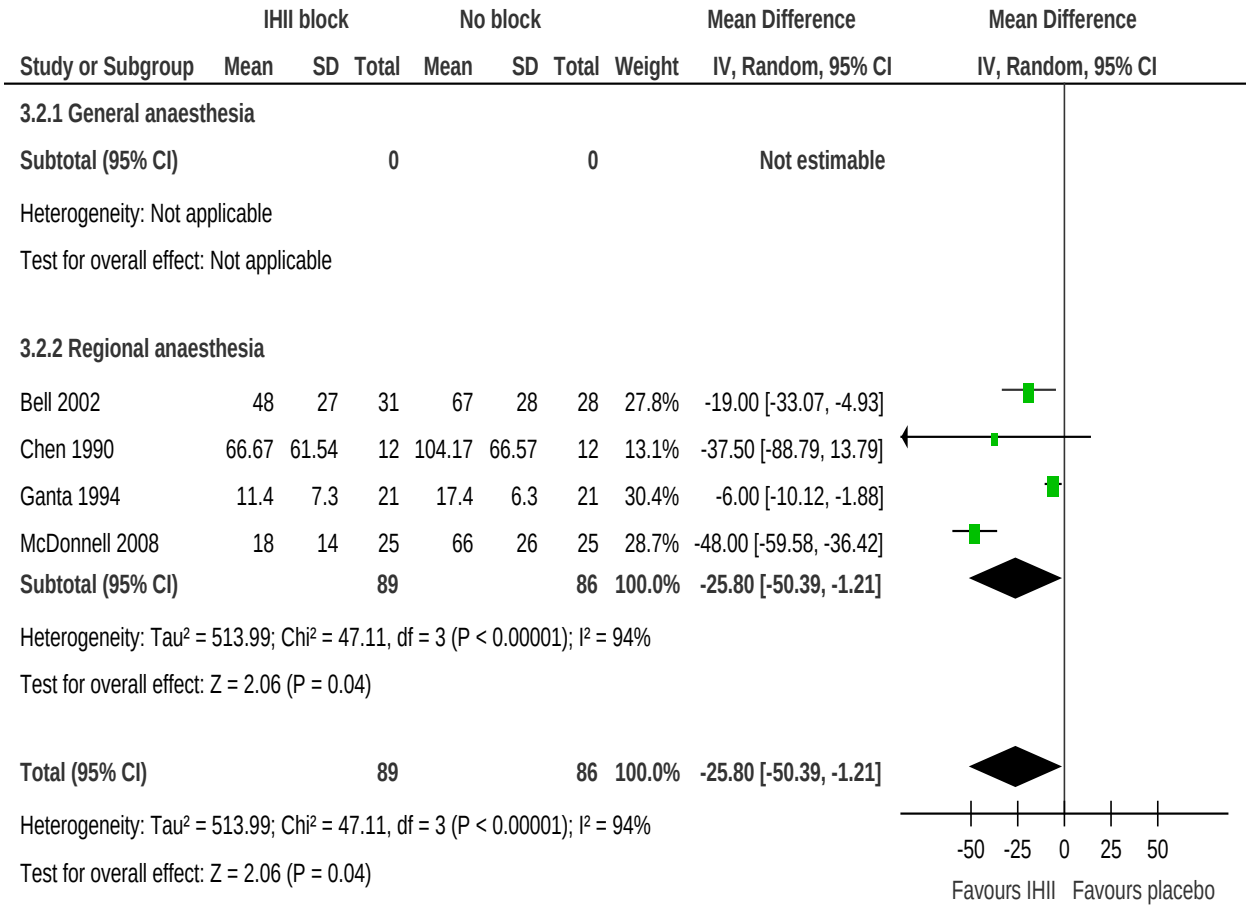
Figure 9 (Analysis 3.1)



Caption

Forest plot of comparison: 4 Abdominal nerve blocks with local anesthetic versus placebo block or no block, outcome: 4.1 Mean visual analogue scale at 24 hours.

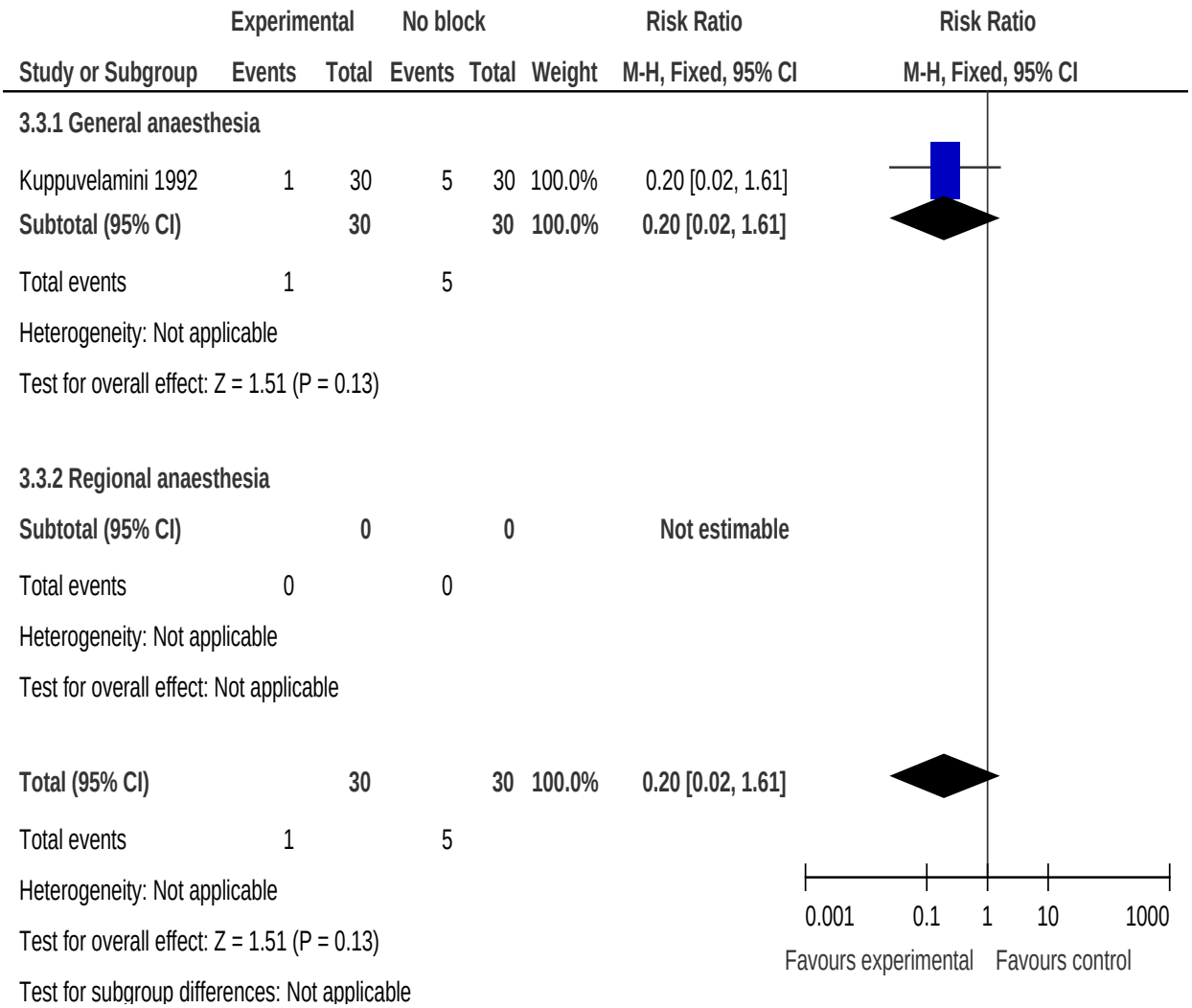
Figure 10 (Analysis 3.2)



Caption

Forest plot of comparison: 4 Abdominal nerve blocks with local anesthetic versus placebo block or no block, outcome: 4.2 Postoperative opioid use (mg) (as defined by trial authors).

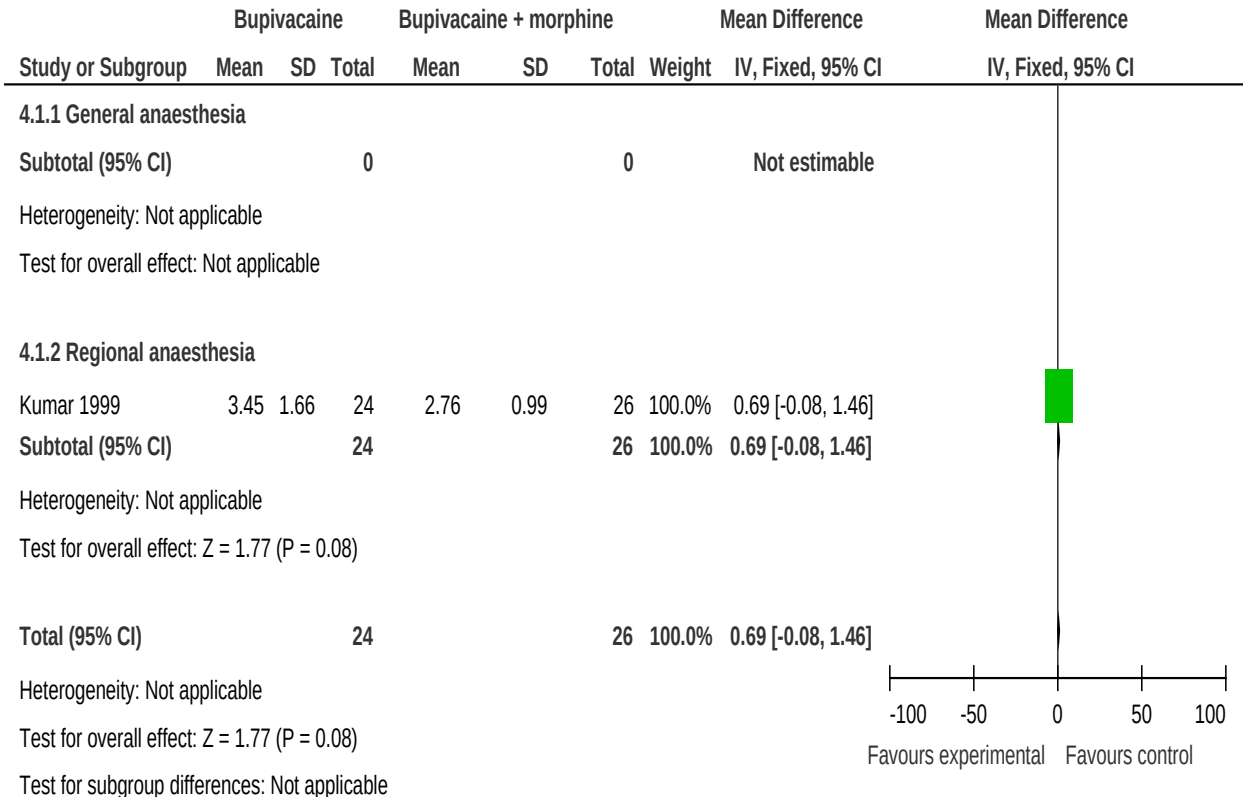
Figure 11 (Analysis 3.3)



Caption

Forest plot of comparison: 4 Abdominal nerve blocks with local anesthetic versus placebo block or no block, outcome: 4.3 No of times mother breast fed in 24 hours.

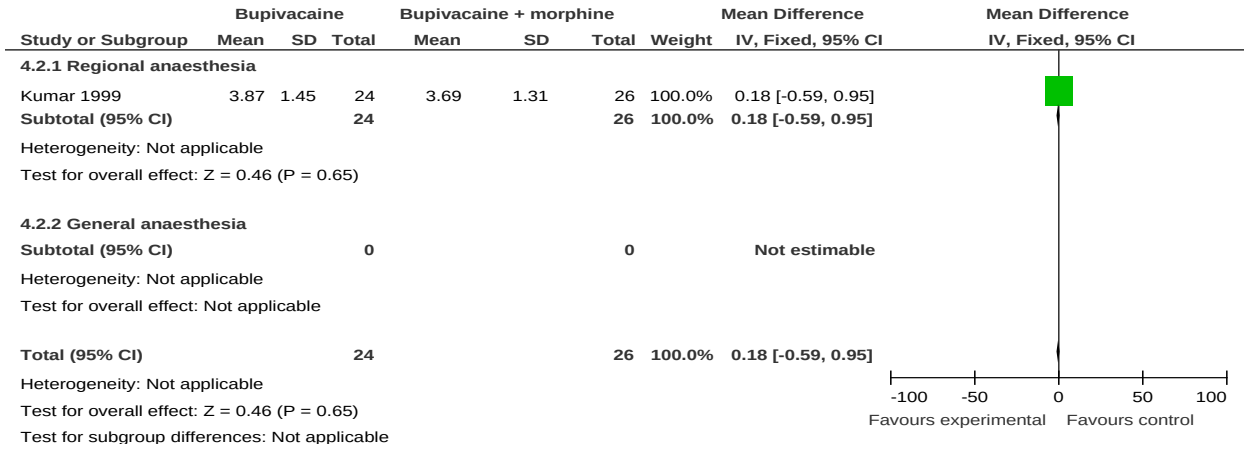
Figure 12 (Analysis 4.1)



Caption

Forest plot of comparison: 5 Wound infiltration with local anesthetic versus local anesthetic + narcotics, outcome: 5.1 Mean visual analogue score at 2 hours.

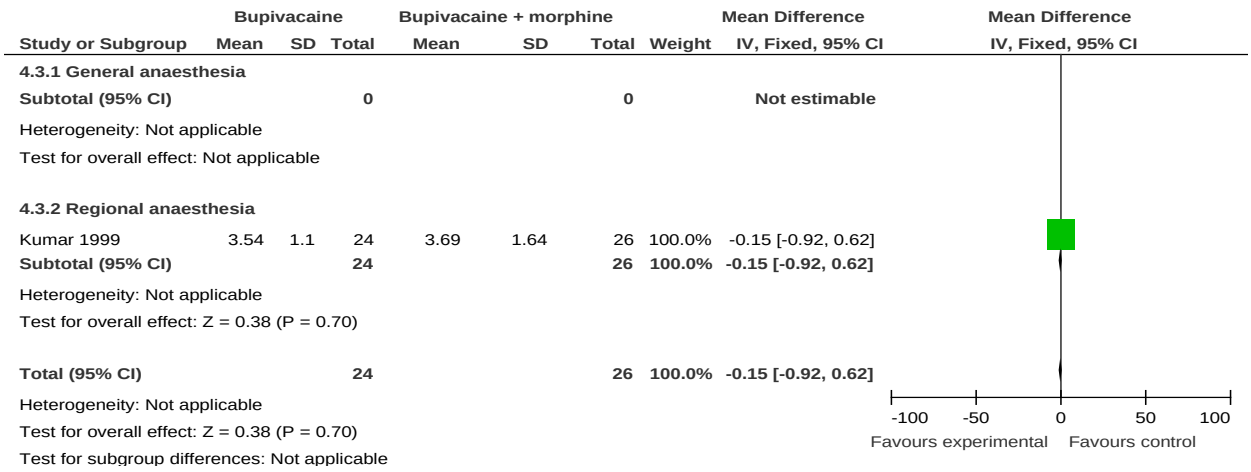
Figure 13 (Analysis 4.2)



Caption

Forest plot of comparison: 5 Wound infiltration with local anesthetic versus local anesthetic + narcotics, outcome: 5.2 Mean visual analogue score at 12 hours.

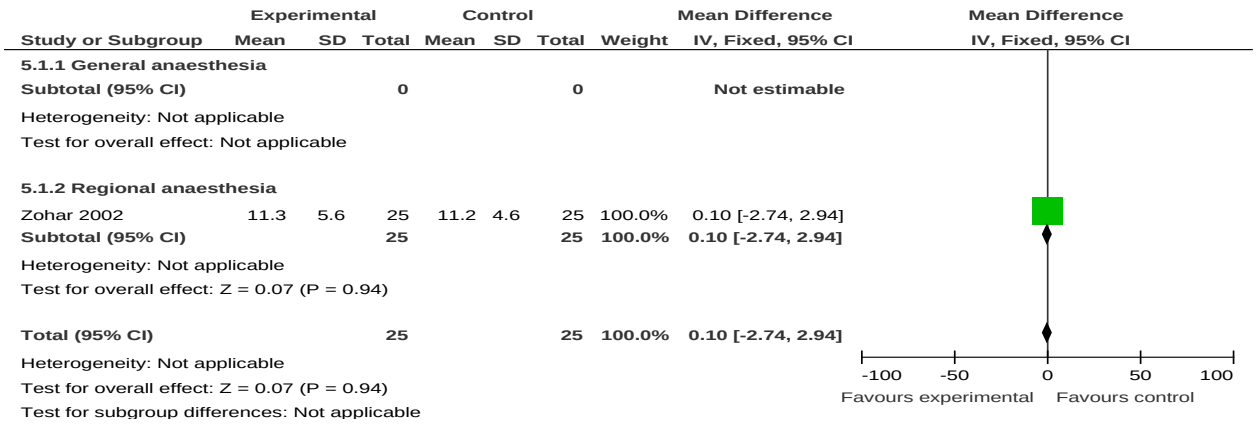
Figure 14 (Analysis 4.3)



Caption

Forest plot of comparison: 5 Wound infiltration with local anesthetic versus local anesthetic + narcotics, outcome: 5.3 Mean visual analogue score at 24 hours.

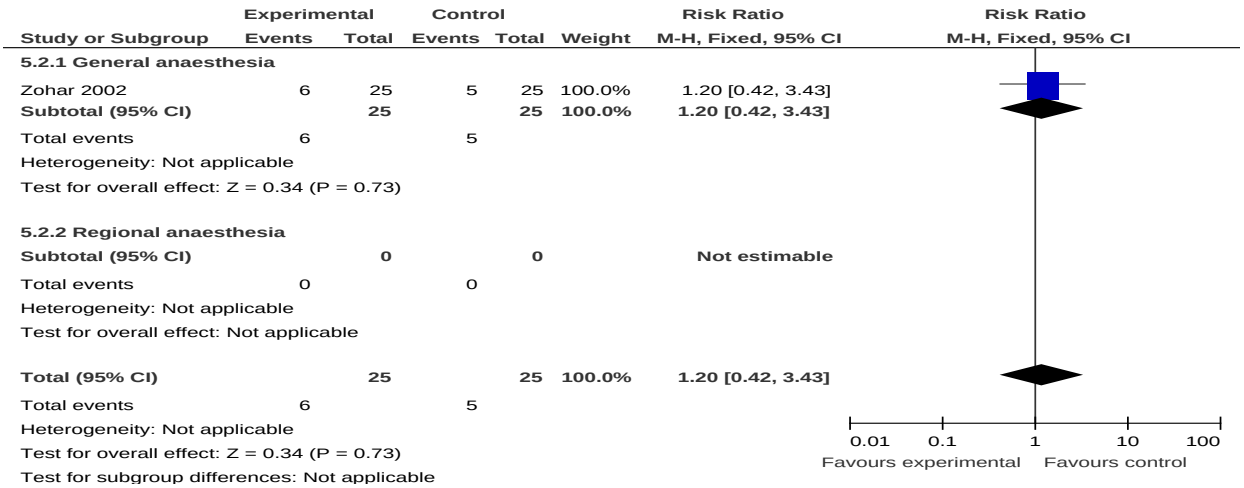
Figure 15 (Analysis 5.1)



Caption

Forest plot of comparison: 6 Wound infiltration with local anesthetic versus local anesthetic + ketamine, outcome: 6.1 Total morphine consumed in the first 6 hours.

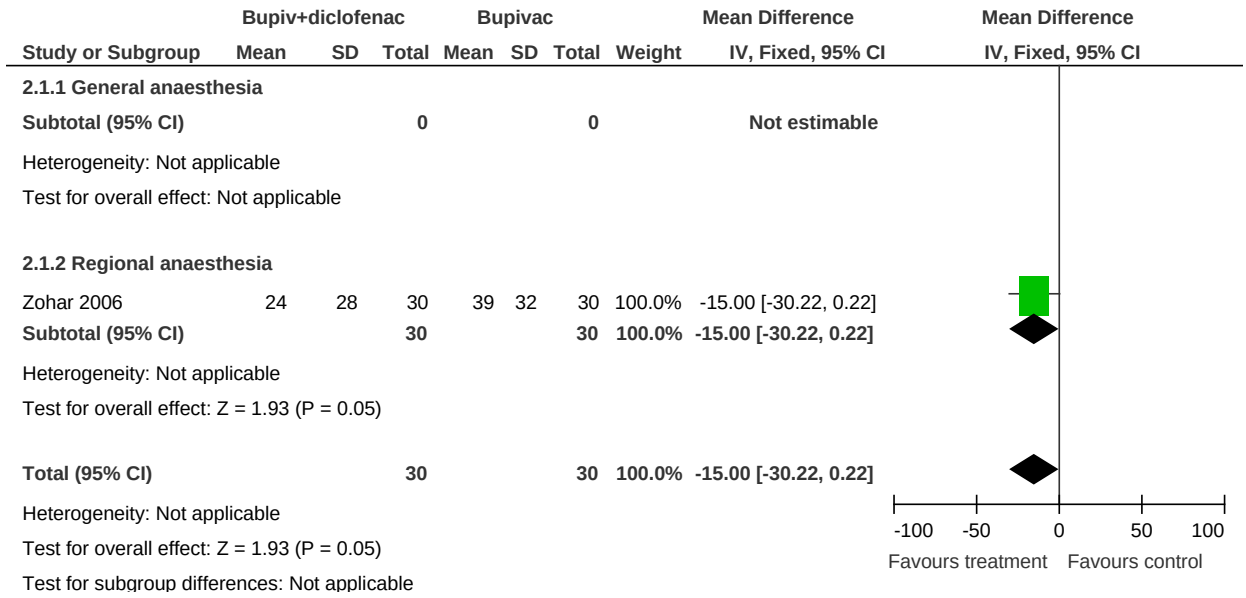
Figure 16 (Analysis 5.2)



Caption

Forest plot of comparison: 6 Wound infiltration with local anesthetic versus local anesthetic + ketamine, outcome: 6.2 Patient satisfaction, good/excellent.

Figure 17 (Analysis 2.1)



Caption

Forest plot of comparison: 3 Wound infiltrations with local anesthetic + non-steroidal anti-inflammatory drugs versus control, outcome: 3.1 No of attempts to activate PCA.

CHAPTER FIVE

SUMMARY, IMPLICATION AND RELEVANCE OF THESIS TO OBSTETRICS PRACTICE

This thesis provides evidence that local anaesthetic infiltration into the caesarean wound as part of multimodal pain strategy, either in general or regional anaesthesia, is of benefit in alleviating post caesarean delivery pain in all settings. The serum level of ropivacaine is within safety margins with the dosage used in the trial and there were no observable side effects in the mothers studied. This dosage can be extrapolated for use in situations where caesarean section needs to be performed under local anaesthetic infiltration only.

5.1 Relevance to obstetrics settings

5.1.1. Magnitude of the problem

On the average around 15% of births worldwide occur by caesarean section. The highest rate (29.2%) is seen in Latin America and the Caribbean, the lowest (3.5%) in Africa. Overall, in developed countries, the proportion of caesarean births is 21.1% [1]. Due to a lack of skill and resources, non-specialist doctors that administer anaesthesia, may be more comfortable performing caesarean sections under general anaesthesia than regional (personal experience). To benefit from local anaesthesia for pain relief, a simple reproducible method of wound infiltration through all layers of the anterior abdominal wound including the peritoneum, was introduced, which will not only block the afferent nociceptive abdominal wall receptors but will also block visceral nerve fibres. With the huge numbers of general anaesthetic caesarean deliveries, especially in resource-constrained settings and worldwide, local anaesthetic into the wound has a positive role to play.

5.1.2. Applicability of the results

The trials included in the systematic review were conducted in a mix of developed and developing countries. The clinical trial was conducted in resource rich settings of a private hospital in a developing country. There is no known reason to expect that the results might have been different if all studies had been conducted in under-resourced hospital settings or in a developed country. Hence, the findings of the systematic review are applicable to all settings. The availability of local anaesthetics may play a role in determining applicability of local anaesthetic wound infiltration.

5.2. Implementation of the intervention

The described method of infiltrating all layers of abdominal wall including spraying/infiltrating the peritoneum in caesarean delivery is an innovation. It is reproducible and may not add excessive cost to health care delivery. The extra cost may be traded off by the amount of opioid spared with the use of local anaesthetic infiltration.

5.3. Research agenda

One of the limitations of this study is the lack of adequate funding to carry out detailed pharmacokinetic trials with an adequate sample size. Only ten patients were sampled and nine patients were analysed. A pharmacokinetic trial that includes free local anaesthetic serum concentration with an adequate sample size is needed.

Studies that directly address the role of anaesthetising the peritoneum by comparing subcutaneous wound infiltration versus LA to all layers including the peritoneum would be helpful.

Pain cannot be quantified hence a cost benefit analysis will be difficult to conduct. However, for purposes of budgeting, a cost benefit analysis study that looks at the materials and the additional time spent on local anaesthetist infiltration, may be worthy of investigation.

Further research may investigate the role of ultrasound guided LA infiltration of the ilioinguinal and iliohypogastric nerves. In addition, sstudies could investigate whether there is any benefit of LA infiltration of the caesarean wound in decreasing chronic pelvic pain. Other areas of interest include pre-incisional infiltration versus post delivery infiltration of caesarean section wounds and the investigation of placental LA concentrations following pre-incision usage compared to plasma levels during epidural use.

The clinical and pharmacokinetic trials carried out for this thesis shed a positive light on the feasibility of conducting well designed trials in private settings in South Africa. Many will believe that carrying out such a study may be met with resistance in the private settings. This was not the case as the patients were well informed, the services of caesarean delivery with the Medi-Clinic protocols were followed and the nursing and the anaesthetic personnel showed high levels of enthusiasm for the study. The overall environment where the study was carried out was welcoming. I recommend that clinical researchers who are in private practise should attempt to conduct their studies in such a set-up.

REFERENCES

1. Betrán AP, Bing-Shun W., Lauer J.A., Merialdi M., Thomas J. & Van Look P. et al. Rates of Caesarean section: analysis of global, regional and national estimates. *Paediatric Perinatal Epidemiology* 2007; 21:98-113.

APPENDIX 1.

PROTOCOLS FOR CLINICAL AND PHARMACOKINETIC TRIALS

PATIENT INFORMATION SHEET – PHARMACOKINETIC STUDY OF ROPIVACAINE FOLLOWING CAESAREAN SECTION WOUND INFILTRATION.

I, Dr A.A. Bamigboye of the Medi-Clinic Hospital and the University of the Witwatersrand, is conducting a study to see whether an injection called ropivacaine, in addition to the normal treatment, reduces the pain that women experience on waking up in theatre after the birth of their babies by caesarean section.

You are kindly invited to participate in the study. If you accept this invitation, the injection will be given at the site of the operation to deaden some nerves in the abdomen after your baby has been delivered. This injection works for about 4-8 hours which is the time of maximum pain after the operation. Some doctors believe the injection reduces pain after the operation. Other doctors believe it does not. One hundred patients have already participated in this study to show whether the medication reduces pain or not. We are still awaiting the result for these patients.

Even though one hundred patients already received this injection during their deliveries as part of this research, and thousands all over the world had received this injection (ropivacaine) following caesarean section, we are yet to measure the amount of ropivacaine in patients who delivered their babies by operation and used this injection to reduce pain. The dose of the injection we shall use is within the recommended level that has been used in adults. We need ten patients to agree to have blood samples taken in order to measure the amount of the injection, ropivacaine, in their blood at different times.

To measure the amount of ropivacaine in your blood, while you are sleeping during the operation, the sleep doctor (anaesthetist) will insert a very small baby plastic needle through which blood will be taken at different

intervals. A teaspoonful (5mls) of blood will be taken from you at 15 minutes, 30 minutes, 60 minutes, 2 hours, 4 hours, 8 hours 16 hours and 24 hours after the operation. The total amount of blood taken will be less than a third of a glass of wine. If this amount of blood is removed in an adult, it does not have any short or long term effect. The blood will thereafter be sent for laboratory analysis.

There may be benefits to participating in this study. The injection that we are studying may decrease the amount of pain that you will experience after the operation. By participating you will be helping to ensure that women, in future, get the best treatment for pain control after caesarean section. This injection, ropivacaine, is not new and has been well used for many years. The few side effects, including allergies, are known, but rare, and treatment of such is available. There is also a possibility of discomfort because of the needle that will be left in your arm for 24 hours and the injection needle site may swell up and rarely be infected. Should you have any of these complaints, we shall act appropriately to correct and treat them.

Any information you provide during the study will be kept confidential. Your name will not appear on any study document and only staff participating in the study will have access to the information you provide. You are free to choose whether or not you wish to participate. You are also free to withdraw from the study at any time should you wish to do so for any reason. If for any reason you are not eligible for the study, or decide not to participate, you will still receive normal care and standard treatment and medications before, during and after birth. We hope you will participate and thank you if you do.

Do you have any questions about the study?

CONSENT

Taking blood for measurement after ropivacaine injection to caesarean section wound to relieve pain.

I have read (or been read to) the information sheet concerning this study and I understand the content of the research. All my questions and doubts have been answered. I understand that I can withdraw from the study at any time I wish, without giving a reason and this will not affect the normal health care I receive.

I would like/ would not like to be informed about the results of the trial (circle or cross)

I… … … … … … … … … … … … … ……. (Participant's full name) agree to take part in this study.

signature……..…..Date…….……

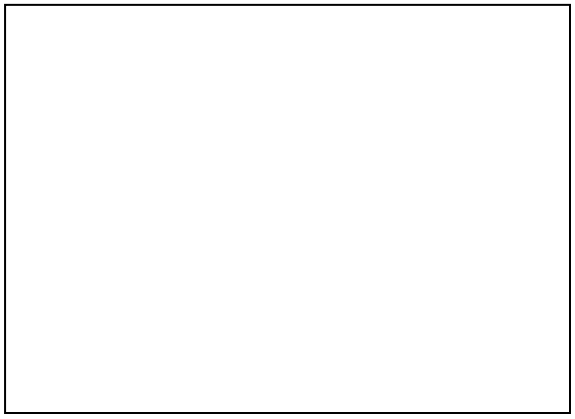
Consenting doctor's name ……..….

Signature…….Date……

PHARMACOKINETIC STUDY RECORD SHEET

Study No…….

Patient's Sticker



Age…….Weight…….Height……Parity…….

Time of Ropivacaine injection----------

Sample time (min)	Time	Signature phlebotomist
Before injection		
15min		
30min		
60min		
2hrs		
4hrs		
8hrs		
16hrs		
24hrs		

INFORMATION LEAFLET AND INFORMED CONSENT

STUDY TITLE: Pre-emptive ropivacaine wound infiltration and peritoneal spraying for post-operative analgesia after general anaesthetic caesarean section.

INVESTIGATOR: DR A.A. Bamigboye

INSTITUTIONS: Nelspruit Medi-Clinic and the University of Witwatersrand

DAYTIME AND AFTER HOURS TELEPHONE NUMBERS: 013 7528274; 0824647142

This consent form may contain words that you do not understand. Please ask me or the study staff to explain any words or information that you do not clearly understand.

You are invited to consider participating in a research study. Your participation in this study is entirely voluntary.

This clinical study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee.

This information leaflet is to help you to decide if you would like to participate. You should fully understand what is involved before you agree to take part in this study. If you have any questions, do not hesitate to ask me. You should not agree to take part unless you are satisfied about all the procedures involved. If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study.

PURPOSE OF THE STUDY AND PROCEDURE

You will be delivering your baby by caesarean section soon under general anaesthesia. I would like you to consider taking part in the research of an injection called ropivacaine (naropin). This injection is used to deaden the area of skin where the operation is done (for example used by dentist to deaden the gum during tooth extraction to prevent or minimise pain).The purpose of this study is to determine whether, if this injection is used on the wound of your operation, it will reduce the amount of pain that you will experience. The study will compare

ropivacaine (naropin) with a placebo, an inactive injection which does not contain any medicine. You will be randomly allocated to one or other treatment (i.e. like spinning a coin). Neither you nor I will know which treatment you are receiving during your participation in the study. This procedure helps to ensure that the information gathered during the study is accurate. In case of an emergency, it will however be possible to determine which treatment you have been receiving.

The study will be performed at the Medi-Clinic private Hospital on one hundred patients undergoing caesarean sections. Your baby will be delivered under general anaesthesia through the abdomen and handed over to the baby doctor (paediatrician) before we inject the wound. This procedure is routinely done by some doctors but we are still not certain if it works. The difference between this procedure and the one routinely done is that all the layers of the abdomen will be injected instead of the skin alone.

Ropivacaine is a well tested injection for blocking pain and even though side effects have been reported when excessive dosages were used, it is the safest of all the local anaesthetic agents. Problems like dizziness, fits and vomiting may occur in patient who are awake and receive overdose or injection into the blood veins but because you will be sleeping under general anaesthesia, this may not show and there are effective measures to treat them. Less than the maximum recommended dose of Naropin will be used. After the operation, we shall be asking you about your pain at intervals and will give you pain injection if necessary. The potential benefit from this study may be less pain after your operation. However, you may not benefit from this study especially if you belong to the placebo (dummy) group but you will receive the usual treatment for pain control. Your participation in this study will contribute to medical knowledge that may help other patients to control their pain after operation. If you decide not to take part in this study you will still receive the best current care for your operation .Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason. Your withdrawal will not affect your access to other medical care. We shall cover the costs of all study

procedures and reasonable medical expenses that you may incur as a direct result of this study. Neither you nor your medical scheme will be expected to pay for any study material or study procedures.

All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.

The 24-hour telephone number, through which you can reach me or another authorised person, is 0824647142.If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2229.

INFORMED CONSENT

I hereby confirm that I have been informed by the study doctor - Dr A.A. Bamigboye about the nature, conduct, benefits and risks of the clinical study of Pre-emptive ropivacaine wound infiltration and peritoneal spraying for post operative analgesia after general anaesthetic caesarean section. I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study. I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report. In view of the requirements of research, I agree that the data collected during this study can be processed in a computerized system. I may, at any stage, without prejudice, withdraw my consent and participation in the study .I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

…… …….. …….

Printed Name Signature / Mark or Thumbprint Date and Time

I, Dr Bamigboye, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

Dr A Bamigboye …… ……..

Printed Name Signature Date and Time

Notes or any other comment

DATA COLLECTION FORM

STUDY NO…

Age	
Weight	
Parity	
No(s) of CS	
Midline or Pfannenstiel incision	
Time skin closed in theatre	
Time in recovery room, when first pethidine was given, if needed	Time when first pethidine given in labour ward
Pethidine needed 1st 1 hr? YES or NO	
Total Pethidine in mg 1st 8 hours	
Total Pethidine needed post operative	
Additional analgesic e.g. VOLTAREN 75 mg imi	

needed?	
RECOVERY ROOM TO COMPLETE	LABOR WARD TO COMPLETE
PAIN 15 MIN. ☐ **Pain score(0-10) = ☐ No pain ☐ mild pain ☐ Severe/unbearable ☐	PAIN 60 MIN ☐ **Pain score (0-10) = ☐ No pain ☐ Mild ☐ Severe/unbearable pain ☐
PAIN 2HRS. ☐ Pain score = ☐ No pain ☐ Mild pain ☐ Severe/unbearable pain ☐	PAIN 4HRS ☐ Pain score= ☐ No pain ☐ Mild pain ☐ Severe/unbearable pain ☐
PAIN 8HRS. ☐ Pain score ☐ No pain ☐ Mild pain ☐ Severe/unbearable pain ☐	PAIN 16HRS. ☐ Pain score ☐ No pain ☐ Mild pain ☐ Severe/unbearable pain ☐
PAIN 24HRS. ☐ Pain score = ☐ No pain ☐ Mild pain ☐	

Severe/unbearable pain ☐	
No of Tramadol/acetaminophen used - 2nd 24hrs.	
Temp above 38 deg celcius-1st 24hrs	Yes ◯ No ◯
Temp above 38 deg celcius-2nd 24 hrs	Yes ◯ No ◯
Any episode of itching	Yes ◯ No ◯
Total No of episodes of vomiting	Yes ◯ No ◯
Septic wound. Please thick	Yes ◯ No ◯
Level of satisfaction of pain control prior hospital discharge. Please tick Excellent/good ◯ Average ◯ unsatisfactory ◯	Level of general post delivery care satisfaction Excellent/good ◯ average ◯ unsatisfactory ◯

ADVERSE EVENTS FORM

STUDY NO:

HOSPITAL NO/STICKER:

DESCRIPTION OF EVENT:

……

……

……

Relation of event to trial medication:

Likely	Unlikely
Not Related	Related

TREATMENT AND/ OR MANAGEMENT OF EVENT

……

……

DATA COLLECTION TABLES

Baseline data, expressed as mean (standard deviation) or proportions (percent). (If distribution not normal, median [interquartile range] will be used).

	Ropivacaine		Placebo	
BASELINE DATA	N		N	
Age (years)				
Primiparous				
Weight				

Outcomes expressed as mean (standard deviation) or proportions (percent)

Outcomes	Ropivacaine		Placebo		Relative risk/mean difference	95% confidence interval
Primary:	N		N			
Need for pethidne within 60 min						
Severe/unbearable pain at 60min						
Secondary outcomes	N					
Mean pethidine used 1st 8hrs						
Mean pethidine used 2nd 8hrs						
Mean pethidine used 3rd 8hrs						
Mean pethidine used in 24hrs						
Severe/unbearable pain at 2 hrs						
Severe/unbearable pain at 4 hrs.						
Severe/unbearable pain						

8hrs.						
Severe/unbearable pain at 16 hrs.						
Severe/unbearable pain at 24 hrs.						
Mean visual analogue score 15min						
Mean visual analogue score 1hr						
Mean visual analogue score 2hrs						
Mean visual analogue score 4hrs						
Mean visual analogue score 8hrs						
Mean visual analogue score 16hrs						
Mean visual analogue score 24hrs						
Mean dosage of pethidine used in 24 hours						
Temp >38deg C						

Total no of tramadol/acetaminophen used						
Level of satisfaction-PAIN						
Level of satisfaction-GENERAL						
Episodes of itching						
Episodes of vomiting						
Any other drug reaction						
Wound infection						

PATIENT INFORMATION SHEET – PHARMACOKINETIC STUDY OF ROPIVACAINE FOLLOWING CAESAREAN SECTION WOUND INFILTRATION.

I, Dr A.A. Bamigboye of the Medi-Clinic Hospital and the University of the Witwatersrand, is conducting a study to see whether an injection called ropivacaine, in addition to the normal treatment, reduces the pain that women experience on waking up in theatre after the birth of their babies by Caesarean section.

You are kindly invited to participate in the study. If you accept this invitation, the injection will be given at the site of the operation to deaden some nerves in the abdomen **after** your baby has been delivered. This injection works for about 4-8 hours which is the time of maximum pain after the operation. Some doctors believe the injection reduces pain after the operation. Other doctors believe it does not. 100 women have already participated in this study to show whether the medication reduces pain or not. We are still awaiting the result for these women.

Even though 100 women already had this injection in this research and thousands all over the world had used this injection following Caesarean section, we are yet to measure the amount of this medicine in women who delivered their babies by operation and used this injection to reduce pain. The dose of the injection we shall use is within the recommended level that has been used in adults. We need 10 women to take blood from and measure the amount of the injection - ropivacaine - in blood at different times.

To measure the amount of the injection in your blood, while you are sleeping during the operation, the sleep doctor (anaesthetist) will insert a very small baby plastic needle through which blood will be taken at different times. A teaspoonful (5mls) of blood will be taken from you in 15 minutes, 30 minutes, 60 minutes, 2 hours, 4 hours, 8 hours 16 hours and 24 hours after the operation. The total amount of blood taken will be less than a third of a glass of wine. If this amount of blood is removed in an adult, it does not have any short or long term effect. The bloods will thereafter be sent for laboratory analysis.

There may be benefits to participating in this study. The injection that we are studying may decrease the amount of pain that you will experience after the operation. By participating you will be helping to ensure that women, in future, get the best treatment for pain control after Caesarean section. This injection (ropivacaine) is not new and has been well used for many years. The few side effects including allergies are known but rare and treatment of such is available. There is also a possibility of discomfort because of the needle that will be left in your arm for 24 hours and the injection needle site may swell up and rarely be infected. Should you have any of these complains we shall act appropriately to correct and treat them.

Any information you provide during the study will be kept confidential. Your name will not appear on any study document and only staff participating in the study will have access to the information you provide. You are free to choose whether or not you wish to participate. You are also free to withdraw from the study at any time should you wish to do so for any reason. If for any reason you are not eligible for the study, or decide not to participate, you will still receive normal care and standard treatment and medications before, during and after birth. We hope you will participate and thank you if you do.

Do you have any questions about the study?

CONSENT

Taking blood for measurement after ropivacaine injection to Caesarean section wound to relieve pain

I have read (or been read to) the information sheet concerning this study and I understand the content of the research. All my questions and doubts have been answered. I understand that I can withdraw from the study at any time I wish without giving a reason and this will not affect the normal health care I receive.

I would like/ would not like to be informed about the results of the trial (circle or cross)

I… … … … … … … … … … … … … ……. (Participant's full name) agree to take part in this study.

signature……..…..Date…….……..

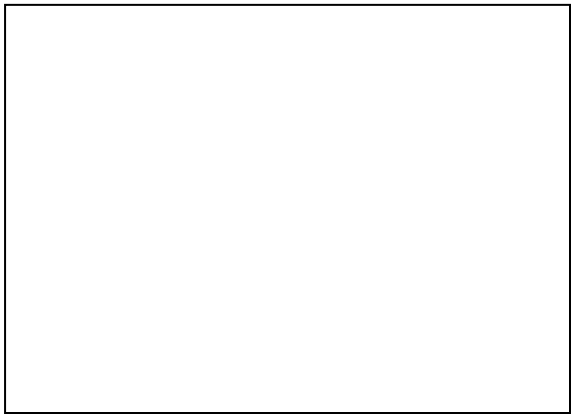
Consenting doctor's name ……..….

Signature…….Date……

PHARMACOKINETIC STUDY RECORD SHEET

Study No…….

Patients Sticker



Age…….Weight…….Height…….Parity…….

Time of Ropivacaine injection----------

Sample time (min)	Time	Signature phlebotomist
Before injection		
15min		
30min		
60min		
2hrs		
4hrs		
8hrs		
16hrs		
24hrs		

APPENDIX 2.

Study identifier: Bamigboye 2008

Review: Local anesthetic wound infiltration and abdominal nerves block during caesarean section for postoperative pain relief

Reviewer: Tess Lawrie

Date: 16 February 2011

Summary:

Methods: RCT conducted in Nelspruit, South Africa. Randomisation by computer-generated list. Allocation concealed in sealed, opaque envelopes. Theatre manager prepared solution. Theatre staff, surgeon and pain assessors were blind to group allocation.

Participants: 100 women undergoing elective CS (50 in each group). Excluded if they did not consent, history of local anesthetic reactions, hypertension in pregnancy with proteinuria, cardiac diseases and any other major medical disorder associated with pregnancy.

Interventions: 30 mls 7.5mg/ml solution ropivacaine or 30 mls normal saline (10 mls sprayed onto divided ages of the peritoneum, 10 mls injected into the edges of the rectus aponeurosis and 10 mls injected subcut along wound edges).Post-op 100mg pethidine every 3-4 hours and 75mg diclofenac every 12 hours were administered as necessary.

Outcomes: Pain assessed by a visual analogue scale at 15 min, 1, 2, 4, 8, 16, and 24 hours post op (dichotomous and continuous variables); pethidine at 1 hour, 8 hours and 24 hours post-op (mean [SD])

In the LA group = significant reduction in severe pain was reported at 15 min and 2 hours post op and significantly less pethidine used at 1 hour post-op.

Notes: Standardised method of general anesthetic and surgical incisions used (pfannenstiel in all but 2 cases). Baseline characteristics were similar.

Decision: A well-designed study that fulfils the inclusion criteria for the above review.

Dr TA Lawrie (MBBCH, PhD, DFSRH)
Systematic reviewer for Cochrane Review Groups
tess@lawrie.com
+44 1225 428021
+44 7826 939464

Assessment of risk of bias:

(1) Sequence generation (checking for possible selection bias)

- adequate (e.g. random number table; computer random number generator; tossing a coin, minimisation);
- inadequate (odd or even date of birth; hospital or clinic record number);
- unclear.

(2) Allocation concealment (checking for possible selection bias)

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- adequate (e.g. where there was no missing data or low levels of missing data (less than 20%) and where reasons for missing data are balanced across groups);
- inadequate (e.g. where missing data are likely to be related to outcomes or are not balanced across groups);
- unclear (e.g. where there is insufficient reporting of attrition or exclusions to permit a judgment to be made).

(5) Selective reporting bias

- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias (For example, if there was extreme baseline imbalance or any other problems that may have had an effect on outcomes)

- yes;
- no;
- unclear.

(7) Overall risk of bias (the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings) low risk of bias

APPENDIX 3.

SOME LETTERS AND CERTIFICATES OF AWARD

Dear Dr Bamigboye,

I thought you would be pleased to know that one of your articles [Local anesthetic wound infiltration and abdominal nerves block during caesarean section for postoperative pain relief., Cochrane Database Syst Rev, 2009] has been selected for Faculty of 1000 Medicine (www.f1000medicine.com) and evaluated by Frederic Mercier see http://www.f1000medicine.com/article/25x4wylm7zkrng4/id/1165629 - Congratulations!

Faculty of 1000 Medicine (www.f1000medicine.com) is a revolutionary literature awareness service that identifies and evaluates the most important articles published in Medicine based on the recommendations of a Faculty of over 2000 peer-nominated leading researchers and clinicians. Your article's identification and inclusion provides recognition from your peers of its scientific merit and the positive contribution it makes to the medical literature.

Many of the world's leading medical institutions already subscribe to Faculty of 1000 Medicine. If your institution does not yet subscribe, you can recommend the service to your librarian using our online form http://www.f1000medicine.com/freetrial/recommendation.

To find out more about Faculty of 1000 Medicine, visit our About Pages at www.f1000medicine.com/about. You can also customize the service to receive tailored e-mail alerts consisting of the articles most relevant to your research interests: just register to use "My F1000" (www.f1000medicine.com/my/) and then select your areas of interest and email preferences.

Finally, don't forget to check out our Hidden Jewels (www.f1000medicine.com/top10/jewels/)

Many congratulations again on your success!

Kind regards,
Anne Greenwood
Managing Director, Faculty of 1000

****
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****

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8 May 2009

Dear Dr Bamigboye

On behalf of the editors of the *International Journal of Gynecology and Obstetrics* (IJGO) and the Executive Board of the International Federation of Gynecology and Obstetrics (FIGO), we are pleased to notify you and your co-authors that your article, "Ropivacaine abdominal wound infiltration and peritoneal spraying at Caesarean delivery for pre-emptive analgesia" has received an Honorable Mention in the John J. Sciarra IJGO Prize Paper Award for 2008. Although the Honorable Mention recognition does not include a financial reward, you and you co-authors will each receive a certificate, which we hope you will be proud to display. As corresponding author, you will be sent the certificates and we ask that you distribute them among your co-authors. Please send your contact address details to Clare Last (Clare@figo.org) at the earliest opportunity.

All clinical research articles from low-income countries that were published during 2008 were considered for this prize. Selection was made by the editors and was endorsed by the IJGO editorial board.

This award was established in 1998 for the purpose of encouraging investigators from low-income countries to submit their best clinical research articles for publication in the IJGO.

The editors of the IJGO and the Executive Board of FIGO extend our congratulations to you and your co-authors on the receipt of this Honourable Mention recognition.

Sincerely,

Timothy R.B. Johnson, MD. Editor

EXCERPTS FROM SOME OF THE INTERVIEWS GRANTED AND PUBLISHED. Assessed on google engine search on 21-03-2010.

Local anaesthetic during C-section curbs later pain

• **Gynaecology news** • Jul 27, 09

Two pain-relieving techniques done during **Caesarean section** may reduce women's need for narcotic painkillers afterward, a research review finds.

After having a **C-section**, women are typically given a combination of painkillers, including opiate drugs such as morphine. But opioids come with side effects like forgetfulness and sedation, and can be transferred to breast milk, leading to drowsiness in the infant.

The new review, of 20 clinical trials, found that adding either of two interventions to standard anaesthesia during **C-section** reduced women's pain and need for opiates after giving birth.

One intervention is known as an abdominal nerve block, in which a nerve- dulling drug is injected into the abdomen before the **C-section** incision is made. The other is called wound infiltration, in which a surgeon irrigates the surgical wound with a solution containing painkillers such as ibuprofen.

Based on the review findings, women planning on having a **C-section** can ask their doctors about having either option, lead researcher Dr. Anthony A. Bamigboye, of the University of Witwatersrand in South Africa, told Reuters Health.

The findings are published in the Cochrane Database of Systematic Reviews, part of the Cochrane Library.

The time immediately after birth is an important period of mother- infant bonding, Bamigboye explained, so new mothers should ideally have the least amount of pain possible and be able to start **breastfeeding** right away.

"Any intervention that can make this goal a reality cannot be overstated," Bamigboye said.

None of the trials in the review tested whether abdominal nerve block or wound infiltration affected women's risk of chronic pelvic pain in the long term. Future studies should look at that question, as well as the costs of local anesthetics, the researchers say.

http://www.bupa.co.uk/individuals/health-information/health-news-index/hi-090709-caesarean-local-anaesthetic

Local anaesthetic during a caesarean reduces need for painkillers

10 July 2009

‘The period immediately after delivery is a significant milestone in the reproductive life of a new mother, and any measure to reduce the unpleasant experience of pain cannot be underestimated’

Dr Anthony Bamigboye, University of Witwatersrand, lead scientist

Having a local anaesthetic during a caesarean, in addition to general or regional anaesthesia, helps manage pain and can reduce how many painkillers you need after the operation, according to a new Cochrane review.

The review, carried out by scientists at the University of Witwatersrand in South Africa, combined the results of 20 studies into the effects of local anaesthetic on pain relief after a caesarean. Altogether, the studies looked at 1,150 women who gave birth by caesarean delivery.

Caesareans are done under regional or general anaesthesia. General anaesthesia means that you will be asleep during the operation. Regional anaesthetic completely blocks feeling from your waist down, but you will stay awake during the operation.

A local anaesthetic can be used during a caesarean, in addition to regional or general anaesthesia. It can be injected into your abdominal (tummy) wall before your skin is cut or after the cut is closed at the end of the operation (abdominal nerve block), or it can be applied directly to the wound (wound infiltration).

The review found that women having a caesarean under regional anaesthesia with local anaesthetic wound infiltration or abdominal nerve block needed fewer painkillers after the operation.

Women having a general anaesthetic and wound infiltration with local anaesthetic needed fewer painkillers during the first 24 hours after the operation. Those who had general anaesthesia and abdominal nerve block had less pain within the first 24 hours.

The scientists concluded that local anaesthesia infiltration or abdominal nerve block, in addition to regional or general anaesthesia, helps to reduce pain after a caesarean.

"It is inevitable to advise physicians performing caesarean sections to use local anaesthetics in addition to pain relief." Dr Anthony Bamigboye, lead author of the review, told the Bupa health information team.

"The period immediately after delivery is a significant milestone in the reproductive life of a new mother, and any measure to reduce the unpleasant experience of pain cannot be underestimated." he said.

Improvements in pain relief can make the time after a caesarean less uncomfortable, allowing mothers to start breastfeeding and bonding with their baby as soon as possible.

Key facts

- A caesarean delivery is an operation to deliver your baby through your abdomen (tummy).
- You may need to have an emergency caesarean delivery or you may plan to give birth this way, for example because you have had previous abdominal surgery.
- Child birth by caesarean delivery is becoming more common. In the UK, about one in five babies are delivered by caesarean.
- If you have a caesarean delivery, you will be given an anaesthetic. You may have a general anaesthetic or a regional anaesthetic. Regional anaesthetics include spinal, spinal epidural or epidural block.
- Pain after a caesarean is controlled with a combination of drugs such as morphine and other pain killers.

Caesarean section: Local anaesthetic reduces need for painkillers post-op

July 7, 2009

Giving a local anesthetic during a Caesarean section helps manage pain after the operation and can reduce consumption of painkillers, according to Cochrane Researchers. The researchers recommend local anesthetics as part of integrated pain management strategies for Caesarean section operations, provided that consideration is given to the cost.

"This review is particularly important in light of the growing number of women giving birth by Caesarean section," says lead researcher, Anthony Bamigboye, of the Department of Obstetrics and Gynaecology at the University of Witwatersrand in Johannesburg, South Africa. "Improved pain relief allows mothers to bond with their babies and begin breastfeeding more quickly."

Caesarean sections account for around a quarter of all births in the US, Canada and the UK. Local anaesthetics can be given, in addition to general or regional anaesthetics, to help manage pain during and after operations. The anaesthetic is either injected to block nerves in the abdominal wall or applied directly to the wound as an anaesthetic solution.

The researchers reviewed data from 20 studies that together involved 1,150 women who gave birth by Caesarean section in both developing and developed countries. They found that women treated with local anaesthetic as well as local or regional anaesthesia did not require as much morphine or other opioid drugs for pain relief after their operations. When non-steroidal anti-inflammatory drugs were also given, pain was reduced further.

One concern, however, is the additional cost of giving local anaesthetic. "None of the trials in this review addressed the cost implications of increasing use of local anaesthetic," says Bamigboye. "A cost benefit analysis is needed to find out whether increased expenditure on theatre time and local anaesthetic can be offset by reductions in postoperative painkillers."

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CLINICAL ARTICLE

Ropivacaine abdominal wound infiltration and peritoneal spraying at cesarean delivery for preemptive analgesia

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Abstract

Objective: To determine whether ropivacaine infiltration into all layers of the abdominal cesarean wound and spraying of the peritoneum decreases postoperative pain. *Methods*: A randomized controlled trial of women undergoing cesarean delivery under general anesthetic allocated to receive either 30 mL of 0.75% ropivacaine or 30 mL of saline into the wound, including spraying of the peritoneum. Postoperative pain and need for rescue opioids were assessed. *Results*: Of the 50 women in the ropivacaine group, 24 (48%) required pethidine or experienced severe pain within 1 hour postoperatively compared with 47 (94%) of 50 women in the control group (relative risk 0.51, 95% CI, 0.38–0.69). The amount of pethidine used in the first hour was reduced in the ropivacaine group (mean difference −58, 95% CI, −73.53 to −42.40). Use of diclofenac and tramadol/paracetamol was also reduced in the ropivacaine group. *Conclusion*: Ropivacaine wound infiltration and peritoneal spraying during cesarean delivery under general anesthetic reduces severe pain and need for opioids.

1. Introduction

Cesarean delivery is a widely performed procedure and rates vary among countries. A figure of 57% has been reported for the private health sector in South Africa [1].

Although spinal and/or epidural block are often the chosen anesthesia used in cesarean delivery, the use of general anesthesia has its indications including abnormal lie, severe antepartum hemorrhage, various contraindications to neuraxial blocks, and patient choice. Management of postoperative pain following cesarean delivery under general anesthesia is mostly multimodal. Opioids have a sedating effect which may impair the early bonding process between mother and newborn.

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Ropivacaine serum concentration following peritoneal spraying and wound infiltration for pain after cesarean delivery

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Multimodal treatment for pain following cesarean delivery can include wound infiltration and peritoneal spraying with ropivacaine hydrochloride [1]. Compared with wound infiltration, peritoneal spraying may allow for greater absorption and serum concentration of the anesthetic agent. The present study was conducted with 10 women who underwent a cesarean delivery at Nelspruit Mediclinic Hospital, South Africa, in 2006. Its objective was to determine serum ropivacaine concentration following administration, by spraying and injection, of 225 mg of the agent to all layers of the anterior abdominal wall and the peritoneum. The study was approved by the Ethics in Human Research Committee of the University of the Witwatersrand.

The procedure for wound infiltration and peritoneal spraying has been previously described [1]. Following delivery of the neonate and placenta and closure of the uterine incision, 10 mL of 0.75% ropivacaine was sprayed onto the edges of the peritoneal wound, 10 mL was infiltrated into the aponeurosis of the rectus muscle, and another 10 mL was injected subcutaneously, for a total of 225 mg. The abdominal wound was then closed with a 2-0 absorbable polyglycolic acid suture. Using an indwelling cannula, venous blood samples were drawn from the antecubital fossa at baseline and 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 16 hours, and 24 hours after the procedure to measure ropivacaine concentration. Two 1-mL specimens were analyzed each time.

Standardization and calibration of the high performance liquid chromatography equipment (Model CCPS; Tosho, Tokyo, Japan) was performed. Serum concentrations were determined by Ampath Laboratory, Pretoria according to the method described by Tanaka et al. [2]. The values were collected on a spreadsheet (Microsoft Excel 2007; Microsoft, Redmond, WA, USA). In cases of protocol violation or sample mix-up the samples were discarded.

The mean ± SD age of the women was 35.4 ± 2.9 years and their mean predelivery weight was 80 ± 18 kg. The maximum serum concentration (C_{max}) of ropivacaine was 1.6 ± 0.9 μg/mL and the time to maximum concentration (T_{max}) was 30 minutes (Table 1). The rapid absorption was due to increased vascularity in pregnancy.

To our knowledge, no pharmacokinetic study of ropivacaine administered by peritoneal spraying has been published. In one study of an epidural block with 150 mg of ropivacaine in women undergoing a

Table 1
Mean serum concentration of ropivacaine at different time intervals in 10 patients who underwent local anesthesia following cesarean delivery

No. of women studied at different time intervals	Time from application, min	Mean ± SD serum concentration, μg/mL
9	0	0
9	15	1.4 (0.6
9	30	1.6 (0.8
8	60	1.3 (0.4
9	120	1 (0.4
7	240	1.1 (0.2
7	480	0.7 (0.5
7	960	0.6 (0.4
6	1920	0.7 (0.7

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Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Bamigboye

CLEARANCE CERTIFICATE — PROTOCOL NUMBER M060623

PROJECT — Pre-emptive ropivacaine wound infiltration and peritoneal spraying for postoperative analgesia after general anaesthetic caesarean section

INVESTIGATORS	Dr A Bamigboye
DEPARTMENT	Obstetrics & Gynaecology
DATE CONSIDERED	06.06.30
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06.07.25 CHAIRPERSON ..... (Professor A Dhai)

*Guidelines for written 'informed consent' attached where applicable

cc Supervisor: Prof GJ Hofmeyr

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10005, 10th Floor, Senate House, University

I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the proposal to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES