LOCAL ANAESTHETIC WOUND INFUSION FOR POSTOPERATIVE PAIN MANAGEMENT FOLLOWING AN ABDOMINAL HYSTERECTOMY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Declaration

I, Hasmita Kooverjee, herewith declare that this research report is my own, unaided work, except where explicit reference is made to the contribution of others. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signed

On this 14 May day of 2025

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Dedication

This research project is dedicated to my loving family, who have always provided unwavering support in all my endeavours.

Presentations and publications from this research project

This article has not been submitted for any publication to date.

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I would sincerely like to thank Dr Anisah Mamoojee and Dr Jacob Moutlana for all their support in aid of completion of this project. Your steadfast belief in me, hard work and perseverance through this unsurmountable journey is genuinely appreciated.

Abstract

Background: An abdominal hysterectomy is one of the most commonly performed major surgical procedures worldwide, used to surgically manage a broad range of gynaecological conditions. It is associated with moderate to severe postoperative pain. Infusion of a local anaesthetic into tissues surrounding the surgical incision, via a multi-lumen indwelling wound catheter may reduce postoperative pain, opioid consumption, opioid related adverse events and the length of hospital stay.

Objectives: To evaluate the efficacy of local anaesthetic wound infusion for postoperative pain management following an abdominal hysterectomy, by assessing pain scores and opioid consumption as the primary objectives.

Methods: We searched the PubMed, Web of Science, MEDLINE Complete, SCOPUS, Cochrane Library and OVID databases from inception until April 2023 to identify trials relevant to this review. We augmented the search by searching reference lists of relevant studies to identify other potential eligible studies. Relevant studies were included based on predetermined inclusion and exclusion criteria. A random effects model of meta-analysis was performed.

Results: This review included six randomised controlled trials that enrolled a total of 244 patients undergoing abdominal hysterectomy comparing infusion of a local anaesthetic to a placebo or sham. In general, studies had no clear risks of bias concerns, except for one study. Wound infusion of local anaesthetic produced a significant reduction in pain at rest [-6.46 (-11.22; -1.70)] and opioid consumption [-21.30 (-34.78; -7.83)] 24 hours post abdominal hysterectomy. The analysis reported no complications associated with the intervention of local anaesthetic infusion. There was no significant reduction in pain on movement 24 hours post-surgery. The included trials varied according to dose, type of local anaesthetic and location of wound catheter. There was significant heterogeneity in the analysis undertaken.

Conclusion: Local anaesthetic infusion post abdominal hysterectomy is a safe and effective way of reducing pain at rest and opioid consumption 24 hours post-surgery. Further research is warranted to assess the true effectiveness of this technique for pain management.

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List of abbreviations

ASA	American Society of Anaesthesiologists Physical Status Classification System
BSO	Bilateral Salpingo-Oophorectomy
CI	Confidence Interval
DF	Degrees of Freedom
ERAS	Enhanced Recovery After Surgery
IM	Intramuscular
IV	Intravenous
JBI	Joanna Briggs Institute
NRS	Numerical Rating Scale
OR	Odds Ratio
PACU	Post-Anaesthesia Care Unit
PCA	Patient Controlled Analgesia
PICO	Problem/Population, Intervention, Comparison, and Outcome
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analysis
RCT	Randomised Controlled Trials
SD	Standard Deviation
TAH	Total Abdominal Hysterectomy
VAS	Visual Analogue Score
VRS	Verbal Rating Scale
WITS	University of Witwatersrand

1. Research report

1.2 Introduction

An abdominal hysterectomy is associated with moderate to severe postoperative pain. (1) It is the most commonly performed major surgical procedure in women worldwide, used to surgically manage a broad range of gynaecological conditions. In the United States of America, more than 500 000 hysterectomies are performed annually. (2) In line with international data, hysterectomies are also one of the most commonly performed surgical procedures in women in South Africa.

Since the advancement of minimally invasive techniques such as vaginal, laparoscopic and robotic assisted hysterectomies, the number of abdominal hysterectomies performed each year has declined. Less invasive approaches provide benefits in terms of reduced pain, earlier mobilisation and quicker recovery. Nevertheless, the abdominal approach remains necessary in many settings, including most emergencies, in patients with malignancies, those with large leiomyomas and in resource limited settings. (3) The most recent audit done by Butt et al (4) showed that the abdominal approach is still the most common surgical approach in South Africa (65.1%).

An abdominal hysterectomy can either be performed via Pfannenstiel incision or less commonly, a midline incision. Both of these methods require dissecting through several layers of the abdominal wall, which is then followed by a pelvic dissection to gain access to the deep pelvic cavity. The abdominal approach provides the benefits of easy, fast and excellent exposure of the abdominal and pelvic cavity. However, this procedure also leads to significant tissue damage resulting in significant pain, which is both visceral and somatic in nature.

Tsui et al (5) demonstrated that adequate postoperative analgesia has been associated with a decreased incidence of cardiopulmonary complications, in-hospital mortality, length of hospital stay and hospital cost. Furthermore, emerging clinical evidence has shown that poorly managed acute postoperative pain can lead to the development of chronic pain. In a recent study done by Beyaz et al, (6) approximately 30% of patients developed chronic pain after undergoing a hysterectomy.

Due to the complex nature of the pain associated with hysterectomies, several different modalities of pain management have been employed. These include, but are not limited to, multimodal analgesia techniques, epidural analgesia, intrathecal analgesia, local anaesthetic infiltration, patient controlled analgesia (PCA) and regional nerve blocks or plane blocks.(2) While useful in their own right, every technique is associated with its own side effects and limitations. It is important to find alternative, synergistic, affordable methods of pain management post abdominal hysterectomy.

Local anaesthetics are a heterogenous group of pharmacological agents that block voltage gated sodium channels, reversibly interrupting the transmission of a nerve impulse in the region in which they are applied. (7) Wound catheter infusion kits are composed of a catheter (a closed-end thin hollow tube with side holes) and an infusion device which can either be an elastomeric balloon pump or an electronic pump. The catheter is placed either in or alongside a surgical wound before closure and a local anaesthetic solution can be administered continuously or repeatedly into the wound (bolus regimen). (8) These catheters can be placed in the sub-peritoneal, pre-peritoneal or subcutaneous layer following abdominal surgery. (9) Continuous wound infusion allows the direct and sustained action of a local anaesthetic within tissues surrounding an incisional wound, inhibiting nociception, and potentially providing analgesia. (10)

When incorporated within a multimodal analgesia protocol, continuous local anaesthetic wound infusion may reduce postoperative pain, opioid consumption, postoperative opioid-related adverse events, and the length of hospital stay. (10) Furthermore, continuous local anaesthetic wound infusion may be an effective alternative to analgesic modalities such as epidural analgesia or peripheral nerve blocks, especially in situations where these techniques are impractical due to resource limitations, difficult anatomy, being poorly tolerated, or contraindicated. (11)

With the trend towards developing pain management strategies that are in line with Enhanced Recovery After Surgery (ERAS) protocols, local anaesthetic wound infusion offers a simple, safe, low cost solution to improving pain management post hysterectomy. Previous systematic reviews looking at the effectiveness of local anaesthetic wound infusions have included a broad range of surgeries; (8) however the validity and relevance of pooling outcomes from different surgical procedures can be viewed as questionable. There is increasing recognition for the need for evidence based guidelines for procedure-specific pain management . At

present, there is no systematic review examining the procedure specific outcomes of local anaesthetic wound infusion after abdominal hysterectomy.

1.2 Aims

The aim of this study was to evaluate the effectiveness of local anaesthetic wound infusions through a wound catheter, compared to a placebo or sham, for postoperative pain management following abdominal hysterectomy.

The search strategy was developed in accordance with the problem/population, intervention, comparison, and outcome (PICO) framework. (12) The population was described as adult patients undergoing abdominal hysterectomy. The intervention included any local anaesthetic at any dose that is continuously infused or delivered through intermittent boluses, through a multi-lumen wound catheter embedded within or adjacent to the surgical wound. The comparator arm was infusion of a placebo such as normal saline or a sham. Lastly, the primary outcomes were postoperative pain at rest and on movement and postoperative opioid consumption at 24 hours.

1.3 Objectives

The **primary objectives** of this study are to determine the effect of local anaesthetic wound infusion on:

1) Postoperative pain at rest and on movement on postoperative day one (24 hours)
2) Postoperative opioid consumption on postoperative day one (24 hours)

(in comparison to placebo or sham)

The **secondary objectives** of this study are to determine the effects of local anaesthetic wound infusion on:

1) Postoperative pain at rest and on movement after postoperative day one (24-48 hours)
2) Postoperative opioid consumption after postoperative day one (24-48 hours)
3) Postoperative opioid related adverse events
4) Length of postoperative hospital stay
5) Major postoperative adverse event

(in comparison to placebo or sham)

1.4 Methods

1.4.1 Protocol and Registration

The study protocol was registered with PROSPERO (CRD42022326662) and adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Supplementary table 1). (13)

1.4.2 Ethics

An ethics waiver was obtained from the University of Witwatersrand's Medical Human Research Ethics Committee (Reference number W-CBP-220620-01).

1.4.3 Eligibility criteria

Articles returned from the electronic literature search of medical databases were assessed for eligibility using the following inclusion and exclusion criteria. The inclusion criteria were :

1) All randomised controlled trials (RCT), including non-standardised designs of RCTs
2) Studies of adult patients (older than 18 years) undergoing abdominal hysterectomy via a lower abdominal midline incision or Pfannenstiel incision
3) Use of any local anaesthetic at any dose that is continuously infused or delivered through intermittent boluses, through a multi-lumen wound catheter embedded within or adjacent to the surgical wound
4) Comparison of the intervention to an infusion of a placebo like saline or a sham
5) Studies which reported on either of the primary outcomes: pain scores or postoperative opioid consumption.

Exclusion criteria were:

1) Patients undergoing other types of hysterectomies (laparoscopic, vaginal, or robotic assisted)
2) Studies that infused agents other than local anaesthetics through the wound catheter
3) Studies in which the comparator arm had no placebo or sham or involved epidurals or peripheral nerve blocks

4) Studies which did not assess the above-mentioned primary outcomes
5) Observational studies.

1.4.4 Data sources

The PubMed, Web of Science, MEDLINE Complete, SCOPUS, Cochrane Library and OVID databases were searched from the inception of the databases until the date of search. The search was performed independently by two authors (HK and AM) between the period of March 2023 and April 2023. The search strategy was developed in consultation with a librarian at the University of Witwatersrand (WITS) Health Sciences library, according to the PICO framework. A detailed list of search terms used in each database is shown in Supplementary table 2 (Supplementary table 2). In addition, the search was augmented by reviewing the reference lists of relevant studies identified through the initial search, to assess for additional studies which could possibly be included.

1.4.5 Data collection

Screening of titles and abstracts were carried out independently by two authors (HK and AM). The results from the database search were exported to a reference manager – Endnote 20 (Clarivate.TM Philadelphia, USA, 2022), after which duplicates were removed. The remaining titles and abstracts were screened according to the predetermined inclusion and exclusion criteria. A full text review was then done on the articles identified through the initial title and abstract screening, to determine final eligibility for inclusion in the review. In addition to the electronic database search, the reference lists of eligible articles were screened to assess for relevant studies which might have been missed by the electronic database search. Full text articles were sought through available databases at WITS and interlibrary loans. In the case of uncertainty of an article's eligibility for inclusion, a third reviewer's opinion was sought (JM).

1.4.6 Data extraction

Data extraction was done independently by two authors (HK and AM). The relevant endpoints were extracted into standardised data extraction sheets, and were then compared to ensure accuracy and completeness.

The following data was extracted from each article:

1) General study details

a) Author
b) Year of study
c) Year of publication
d) Country of origin of the study
e) Location of study and number of centres
f) Study inclusion and exclusion criteria
g) Funding sources

2) Participants
    a) Sample size (including sample allocated and analysed in each group)
    b) Indication and urgency of hysterectomy
3) Intervention
    a) Type and size of incisional wound
    b) Location and type of wound catheter
    c) Type and strength of local anaesthetic in the intervention group
    d) Rate and duration of wound infusion, or intermittent bolus regimen
4) Control
    a) Details of placebo or sham used in the control group
    b) Perioperative analgesic co-interventions and adjuncts, including rescue analgesia
5) Outcomes measured in order to assess primary and secondary objectives of this systematic review
    a) Primary objectives
        i) Postoperative pain at rest and on movement on postoperative day one (24 hours)
        ii) Postoperative opioid consumption on postoperative day one (24 hours)
    b) Secondary objectives
        i) Postoperative pain at rest and on movement after postoperative day one (24-48 hours)
        ii) Postoperative opioid consumption after postoperative day one (24-48 hours)
        iii) Postoperative opioid related adverse events
        iv) Length of postoperative hospital stay
        v) Serious postoperative adverse events

1.4.7 Risk of bias assessment

The risk of bias and quality of the included studies were assessed using the revised JBI critical appraisal tool for assessment of risk of bias for RCTs (Supplementary table 3). (14) It is a

fixed, structured tool that assesses 13 domains to determine both the internal validity and statistical conclusion validity of the study. The following domains are assessed:

1) Was true randomization used for assignment of participants to treatment or control groups?
2) Was allocation to the treatment group concealed?
3) Were treatment groups similar at baseline?
4) Were participants blinded to treatment assignment?
5) Were those delivering treatment blind to treatment assignment?
6) Were outcome assessors blind to treatment assignments?
7) Were treatment groups treated identically other than the intervention of interest?
8) Was follow up complete? If not, were differences between groups in terms of their follow up adequately described or analysed?
9) Were participants analysed in the groups to which they were randomized?
10) Were outcomes measured in the same way for treatment groups?
11) Were outcomes measured in a reliable way?
12) Was appropriate statistical analysis used?
13) Was the trial design appropriate, and any deviation from the standard RCT design accounted for in the conduct and analysis of the trial?

Each domain was assessed as yes, no, unclear or not applicable. All studies were included irrespective of their risk of bias assessment.

1.4.8 Summary of measures and synthesis or results

All statistical analyses were performed using the software package R V4.3.1(R: A Language and Environment for Statistical Computing, R Core Team, 2023). All continuous data (pain scores, opioid consumption and length of hospital stay) were reported as mean and standard deviation (SD). The mean difference (MD) between the intervention and control groups was used as measure of effect size because of its interpretability. For continuous data, the accompanying 95% confidence interval (CI) and p-value were presented. A p-value of < 0.05 was considered statistically significant. If the p-value was less than <0.01, this was specifically indicated on the forest plot.

All pain intensity data were presented as mean scores out of 100: 100mm Visual Analogue scale (VAS). Where pain intensity data were reported on 0-10 rating scales, the results were converted to a score out of 100 by multiplying by 10. Where pain intensity data were reported

as a median, the mean and SD were estimated using the Box-Cox power transformation method of mean estimation; and the standard deviation estimated from quantiles. (15) In studies where pain intensity data were reported as the mean and 95% confidence interval of the mean, the 95% CI was converted to a SD using the method suggested in the Cochrane Handbook for Systematic Reviews of Interventions, assuming a t-distribution. (16)

All opioid use data were converted to milligrams of morphine equivalents.

For dichotomous data, such as opioid related adverse events and major adverse events, percentage incidence of the events and an odds ratio was used to present the data.

Despite the small number of studies and significant methodological heterogeneity between studies (see Table 1), a meta-analysis was undertaken using a random effects model. We used the I^2 and Tau^2 (τ^2) test to assess for heterogeneity between studies. The I^2 test was used to assess whether variance in effect sizes between studies was by chance (sampling error) or because of systematic differences between studies (study heterogeneity). High values indicated that there were systematic differences between the studies and that a random effects model should be used. The Tau^2 test was used with the random effects models to express the extent of the variance between effect sizes across the studies included in the meta-analysis. The Chi^2 (χ^2) test was used to assess for differences in subgroup analysis.

1.5. Results

1.5.1 Study selection

Figure one shows the PRISMA flow diagram detailing the study selection process. The initial search strategy of databases identified 6930 articles. Screening the reference lists yielded one additional article. After removing duplicates, 1440 articles remained for title and abstract screening. 1429 articles were subsequently excluded as they did not meet the relevant inclusion and exclusion criteria. The remaining 11 articles that warranted a full text review were sought for retrieval. A further five studies were excluded for the following reasons: four articles had no placebo/sham control arm and one study included different types of gynaecological surgeries with no subgroup analysis. The final systematic review compromised of six eligible articles.

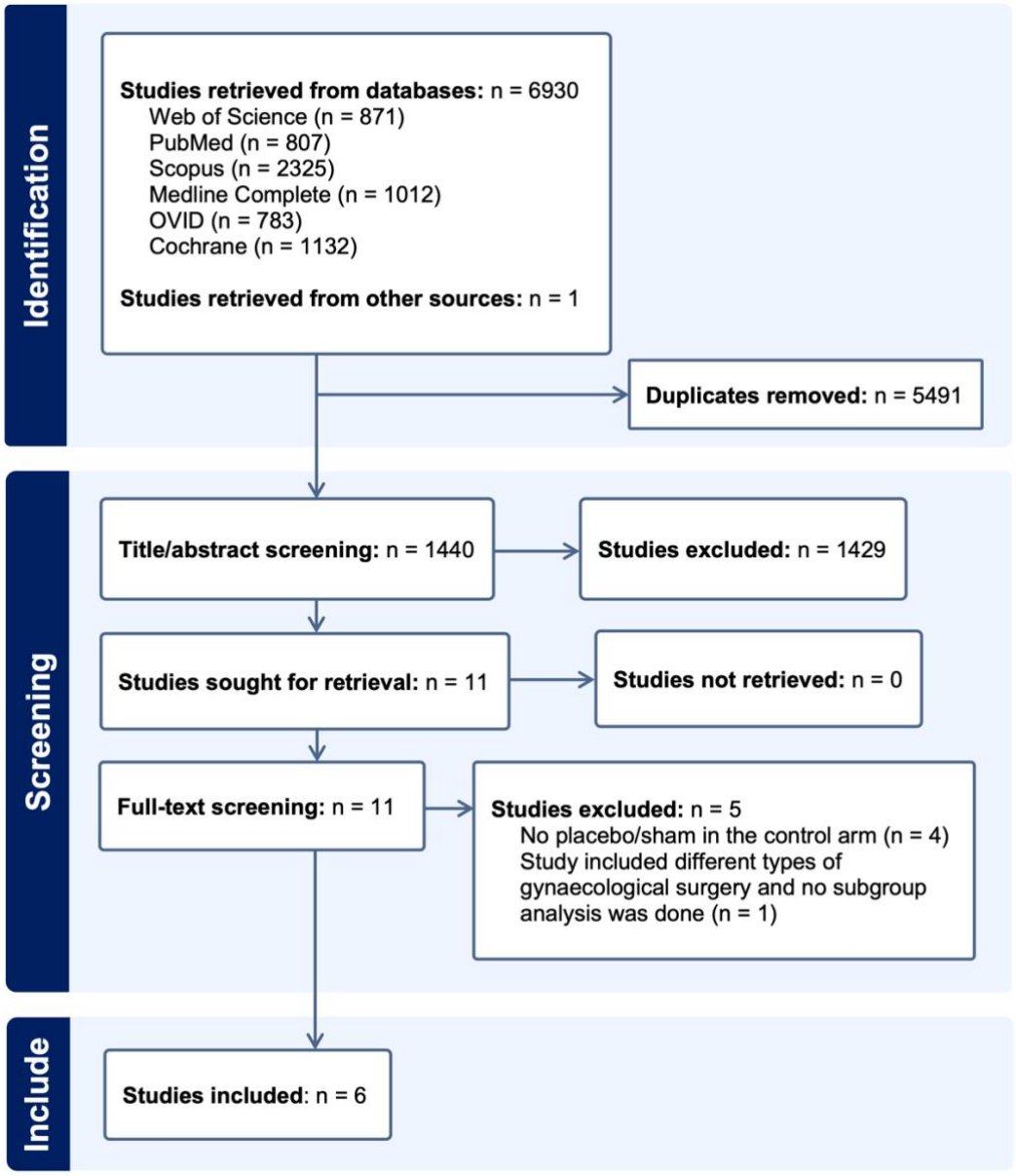

Figure 1. Prisma flow diagram

1.5.2 Study characteristics

The characteristics of the six included studies are presented in Table 1. In summary, the six studies took place from 1999 to 2014, across five countries. All studies involved a single study site. Samples sizes were modest (total sample size range: 36 to 50). The combined sample size of patients included in the review was 244. The majority of studies, 66.6%, only included patients presenting for elective surgery. Two studies did not report on the urgency of surgery in the participants. The Pfannenstiel approach was the most common incision type, with 50% of studies only including this surgical approach. The local anaesthetic used was Bupivacaine (0.25% or 0.39%) in three studies, Levobupivacaine (0.25%) in two studies, and

Lidocaine (0.5%) in one study. Five studies used saline infusion as a control, while one study used a sham (catheters not placed in the wound). With regards to catheter placement, heterogeneity was noted with regards to the number of catheters and location of catheter placement. Of the six included studies, two studies had sub-peritoneal catheters, three had subcutaneous catheters and one study had both a subcutaneous and pre-peritoneal catheter. There was also significant heterogeneity between the studies in terms of the local anaesthetic and saline infusion rate or bolus administration, and the use of rescue medication. In terms of outcome measures, pain was reported in two studies using a 10cm Visual Analogue Scale (VAS), in two studies using a 100mm VAS, in one study using a 10 point Numerical Rating Scale (NRS) and in one study using a five-point Verbal Rating Scale (VRS). For the outcome measure of opioid consumption, four studies measured milligrams of morphine consumption, one study measured milligrams of ketobemidone consumption and one study measured both morphine and meperidine consumption.

Table 1. Characteristics of studies included in the systematic review

Author	Year	Country	Study sites (N)	Randomised (N)	Analysed (N)	Inclusion criteria	Exclusion criteria
Kristensen et al.	1999	Denmark	1	Intervention: 22 Control: 20	Intervention: 21 Control: 19	ASA I and II; elective abdominal hysterectomy	Allergy to bupivacaine; < 18 years old; regular use of opioid analgesics
Zohar et al.	2001	Israel	1	Intervention: 18 Control: 18	Intervention: 18 Control: 18	ASA I, II, and III	Significant cardiovascular, pulmonary, hepatic, renal, neurologic, psychiatric, or metabolic disease
Gupta et al.	2004	Sweden	1	Intervention: 20 Control: 20	Intervention: 20 Control: 20	Not reported	Undergoing surgery for cancer; receiving analgesic medication chronically
Marić et al.	2009	Croatia	1	Intervention: 25 Control: 25	Intervention: 25 Control: 25	ASA I, II, and III; undergoing TAH and BSO via Pfannenstiel incision	Significant cardiovascular, pulmonary, hepatic, renal, neurologic, psychiatric, or metabolic disease; obesity; chronic pain
Russell et al.	2011	South Africa	1	Intervention: 18 Control: 18	Intervention: 18 Control: 18	ASA I and II; elective TAH; Pfannenstiel incision	Contraindication to general anaesthesia; allergy to any of study medications; history of drug or alcohol abuse; major medical disease such as: cardiovascular, pulmonary, metabolic, renal, neurological, or psychiatric disease
Perniola et al.	2014	Sweden	1	Intervention: 20 Control: 20	Intervention: 20 Control: 20	ASA I and II; patients aged 30-75 years; elective hysterectomy with or without BSO	Chronic pain treated with opioid analgesics; atrioventricular block; being treated with class III antiarrhythmics; severe hepatic or renal disease

Table 1 continued

Author	Year	Surgical urgency	Type of incisional wound (N)	Location and type of wound catheter	Infusion agents Control/ sham procedure
Kristensen et al.	1999	Elective	Pfannenstiel (24); midline (17)	Two sub-peritoneal infiltration catheters (PBN Medicals): 1.2 mm in outside diameter, 600 mm long, 90 side holes spaced 0-450 mm from tip	Intervention: Bupivacaine 0.25% Control: Saline
Zohar et al.	2001	Not reported	Pfannenstiel (36)	Subcutaneous, multi-holed 20 G epidural catheter	Intervention: Bupivacaine 0.25% Control: Saline
Gupta et al.	2004	Elective	Pfannenstiel (10); midline (30)	Subcutaneous, multi-holed catheter	Intervention: Levobupivacaine 0.25% Control: Saline
Marić et al.	2009	Not reported	Pfannenstiel (50)	Subcutaneous, multi-holed 20 G epidural catheter	Intervention: Levobupivacaine 0.25% Control: Saline
Russell et al.	2011	Elective	Pfannenstiel (36)	Two catheters (one subcutaneous, one pre-peritoneal) “On-Q PainBuster Soaker 6.5 pain relief system” (multi-holed catheter)	Intervention: Bupivacaine 0.39% Sham: Catheter positioned on top of wound, covered by sterile bandage. Catheter connected to similar apparatus as trial group, but did not penetrate wound or deliver any substance
Perniola et al.	2014	Elective	Pfannenstiel; midline (sample sizes not reported)	One sub-peritoneal “On-Q PainBuster Soaker 6.5 pain relief system” (multi-holed catheter)	Intervention: Lidocaine 0.5% Control: Saline

Table 1 continued

Author	Year	Rate and duration of wound infusion, or intermittent bolus regimen	Perioperative analgesic co-interventions and adjuncts, including rescue analgesia
Kristensen et al.	1999	15 ml of 0.25% (2.5 mg/ml) into each catheter = 37.5 mg into each catheter 4-hourly (total 75mg 4-hourly) for 48 hours	Morphine 0.15 mg/kg IM injection or morphine 0.075 mg/kg IV injection
Zohar et al.	2001	PCA delivers 9 ml of 0.25% bupivacaine (22.5 mg) with a 60-minute lockout	Diclofenac 75 mg (all patients); Rescue analgesia: Morphine 2 mg IV injection if VAS > 40 mm 20 minutes after initiating PCA device, followed by 2 mg of morphine IV injection repeated at ten-minute intervals until VAS ≤ 30 mm
Gupta et al.	2004	Bolus of 20 ml of 0.25% (50 mg), followed by infusion 5 ml/hr of 0.25% levobupivacaine (12.5 mg/hr)	Ketobemidone 1-2 mg IV during the first 4 hours in the PACU. Thereafter PCA pump with ketobemidone (1 mg bolus, 6 min lockout) for pain ≥ 3 on an NRS
Marić et al.	2009	7 ml/hr of 0.25% levobupivacaine (17.5 mg/hr)	Diclofenac 75 mg IV and morphine 0.1 mg/kg IV injection 30 minutes before the end of surgery (all patients). After extubation pain was assessed, and if VRS > 2, then 2 mg of bolus morphine given every 5 minutes until VRS was 1. Thereafter, patient given a PCA, set to deliver 1 mg of morphine with ten-minute lockout
Russell et al.	2011	Initial 5 ml bolus of 0.5% bupivacaine into each catheter (50 mg), followed by 0.39% bupivacaine at 4 ml/hr for 30 hours (15.6 mg/hr)	PCA pump set to deliver 1 mg/ml morphine with 6-minute lockout. After the PCA was removed, diclofenac 100 mg suppositories given every 18 hours and paracetamol 1 g every six hours
Perniola et al.	2014	Infusion of 10 ml of 0.5% lidocaine every hour (50 mg/hr) and IV saline 10 ml/hr	Rescue morphine in the first four hours so that NRS ≤ 3. Thereafter, 1 mg morphine administered via PCA pump with 6-minute lockout

Table 1 continued

Author	Year	Outcomes measured				
		Pain scores	**Opioid consumption**	**Opioid related adverse events**	**Length of hospital stay**	**Major adverse events**
Kristensen et al.	1999	10 cm VAS Pain at rest: 4, 22, 28, 46 and 52 hours Pain on movement (coughing): 4, 22, 28, 46 and 52 hours	Milligrams of morphine 0-24 hours 24-52 hours	Not reported	Not reported	Wound infection Other complications (not specified)
Zohar et al.	2001	100mm VAS Pain at rest: 1, 2, 3, 4, 5, 6 and 24 hours Pain on movement: 1, 2, 3, 4, 5, 6 and 24 hours	Milligrams of morphine or meperidine Morphine: 6 hours Meperidine: 18 hours	Incidence of nausea	Not reported	Not reported
Gupta et al.	2004	10cm VAS Pain at rest (incision site): 1, 2, 3, 4, 8, 16 and 24 hours Pain on movement (coughing): 1, 2, 3, 4, 8, 16 and 24 hours	Milligrams of ketobemidone 0-4 hours 4-24 hours 0-24 hours	Incidence of nausea and incidence of vomiting 0-4 hours 4-24 hours	Median number of days	Wound infection Local anaesthetic toxicity Side effects (not specified)
Marić et al.	2009	5 point VRS Time frame and pain on rest/movement not specified	Milligrams of morphine 0-6 hours 0-48 hours	Incidence of nausea	Not reported	Not reported
Russell et al.	2011	100mm VAS Pain at rest: 1, 6, 24, and 30 hours Pain on movement: 1, 6, 24, and 30 hours	Milligrams of morphine 0-1 hour 1-6 hours 6-24 hours 24-30 hours	Incidence of nausea or vomiting and incidence of pruritis	Not reported	Not reported
Perniola et al.	2014	10 point NRS Pain at rest (incision site): 1, 4, 8, 24 and 48 hours	Milligrams of morphine 0-4 hours 4-24 hours 24-48 hours 0-24 hours	Incidence of nausea and incidence of vomiting 0-4 hours 4-24 hours 24-48 hrs	Median number of days	Local anaesthetic toxicity

		Pain on movement (coughing): 1, 4, 8, 24 and 48 hours				

ASA: American Society of Anaesthesiologists Physical Status Classification System; BSO: Bilateral Salpingo-oophorectomy; IM: Intramuscular; IV: Intravenous; NRS: 0-10 Numerical Rating Scale; PACU: Post-Anaesthesia Care Unit; PCA; Patient-Controlled Analgesia; TAH: Total Abdominal Hysterectomy; VAS: Visual Analogue Scale 10cm or 100mm; VRS: 0-5 point Verbal Rating Scale; NRS 0-10 point Numerical Rating Scale

1.5.3 Risk of bias assessment

The risk of bias assessment is reported in Figure 2. In general, studies had no clear risks of bias concerns, except the study by Russell et al. (17) In that study, allocation to the treatment group was not concealed, the investigators delivering the intervention were not blinded to the intervention, and investigators collecting the data were not blinded to the intervention. The worst performing risk of bias category was whether follow-up was complete, with two studies not demonstrating complete follow-up (Kristensen et al. 1999; Perniola et al. 2014) and three studies being unclear on whether follow-up was complete (Gupta et al. 2004; Marić et al. 2009; Zohar et al. 2001). (18-22) Assessing outcomes in the context of risk of bias scores, indicated no clear relationship between the risk of bias score and outcomes (data not shown).

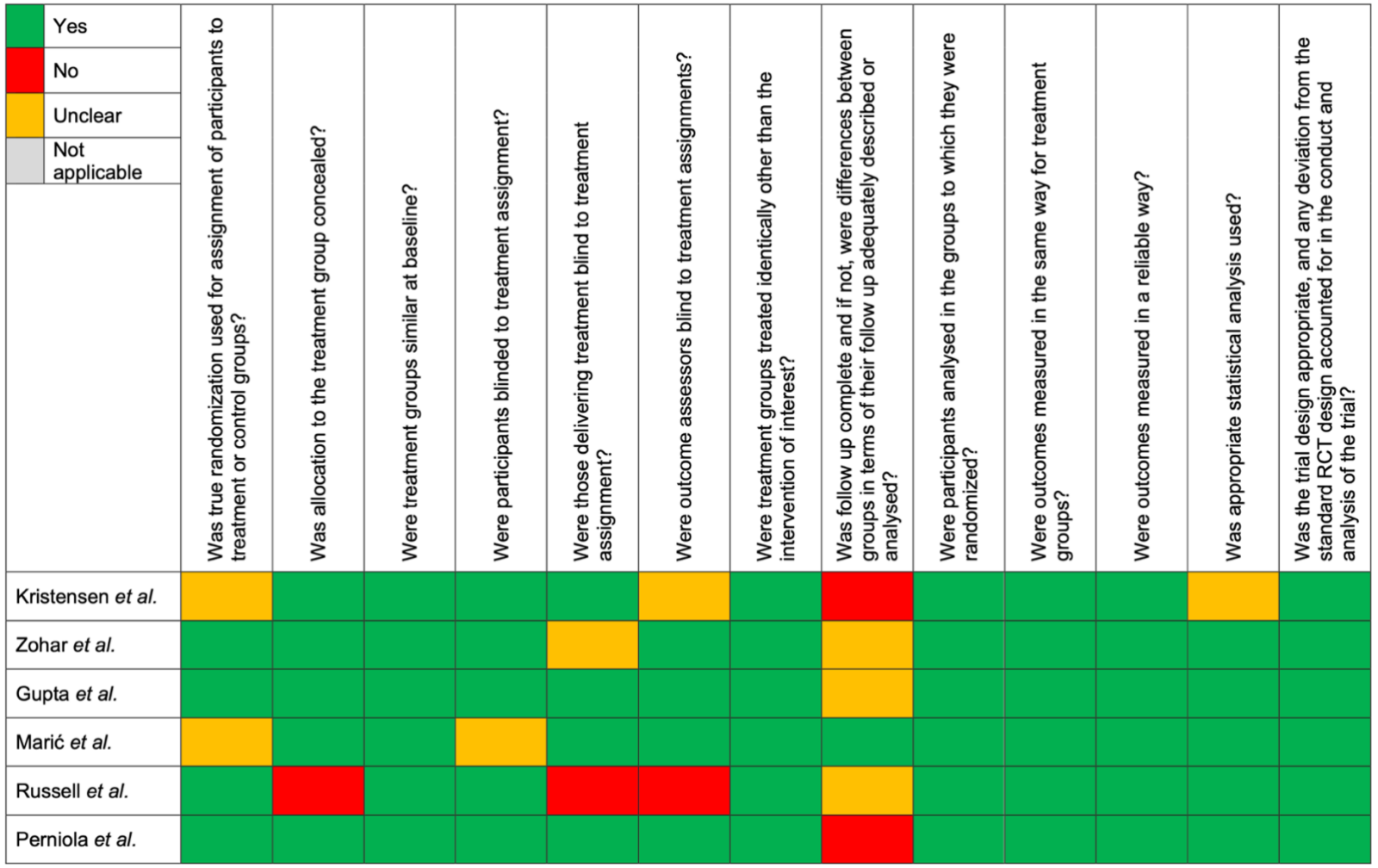

Figure 2. Risk of bias assessment

1.5.4 Results and synthesis of individual study data

Supplementary table 4: Evaluation of data availability to assess the primary and secondary objectives.

Postoperative pain at rest on postoperative day one (24 hours)

The difference in means for the four studies with usable data is shown below in Figure 3. The point estimate for all studies showed less pain at rest in the intervention group compared to the control/sham group, but the effect sizes were small; a difference of means of 11 points on a 100-point scale was the largest effect (Zohar et al. 2001). (22) When examining the range of plausible values for the studies (95% CI), all studies showed a lack of precision. (17, 19, 20) Overall, the random effects model returned a point estimate mean difference across the studies of -6.46 (in favour of the intervention) with a 95% CI of -11.11 to -1.70. Thus, the plausible range of effect sizes was consistent with a small effect in favour of the intervention, which is statistically significant. There was no significant differences between the intervention sub-groups (Bupivacaine, Levobupivacaine, Lidocaine).

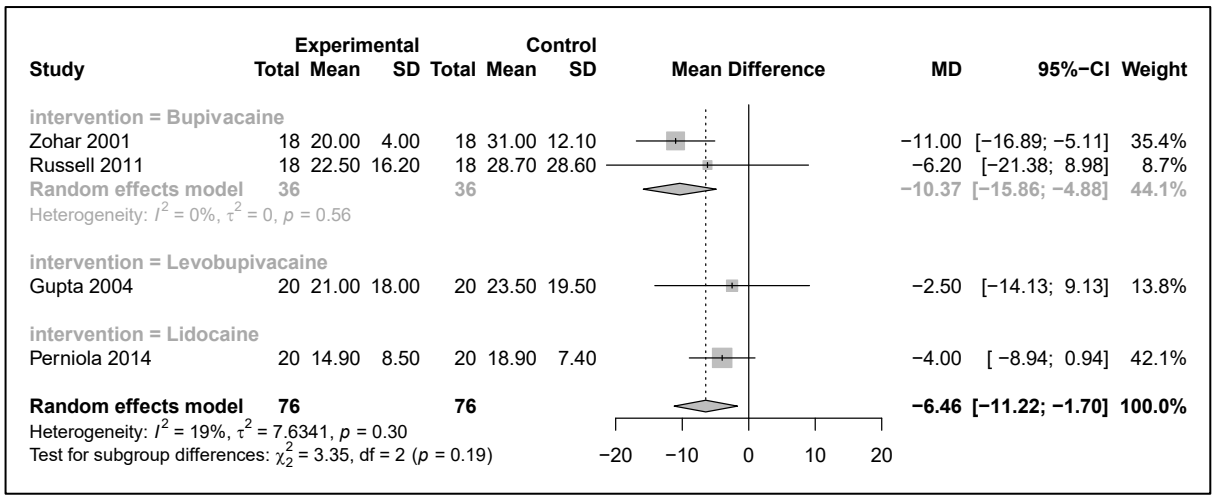

Figure 3. Difference in means for pain at rest on postoperative day one (measured 24 hours after surgery)

Pain intensities were reported using a 100-point scale, with 0 being no pain. Negative values indicate less pain at rest in the intervention group compared to the control/sham group. MD: Mean difference, 95%-CI: 95% confidence interval, df: degrees of freedom.

Postoperative pain on movement on postoperative day one (24 hours)

The difference in means for the four studies with usable data are shown in Figure 4. The point estimate for two studies (Russell et al. 2011; Zohar et al. 2001) showed fairly robust decreases in pain with movement in the intervention group compared to the control/sham group (approximately 20 points on a 100-point scale), but the upper bound of the 95% CI indicated that the data were consistent with there being small effects. (17, 22) Counter to these two studies, the study by Gupta et al (20) showed the opposite effect (i.e. pain in the control/sham group being less than that of the intervention group). One study showed almost no difference in pain intensity between the groups (Perniola et al. 2014). (19) Overall, the random effects model returned a point estimate mean difference across the studies of -5.29 (in favour of the intervention) with a 95% CI of -25.30 to 14.73. These findings are consistent with a small, but insignificant, decrease in pain on movement in the local anaesthetic group compared to the control group. A high level of heterogeneity between studies should also be noted, further reducing the statistical validity of these results. There was a significant difference between the intervention sub-groups (Bupivacaine, Levobupivacaine, Lidocaine).

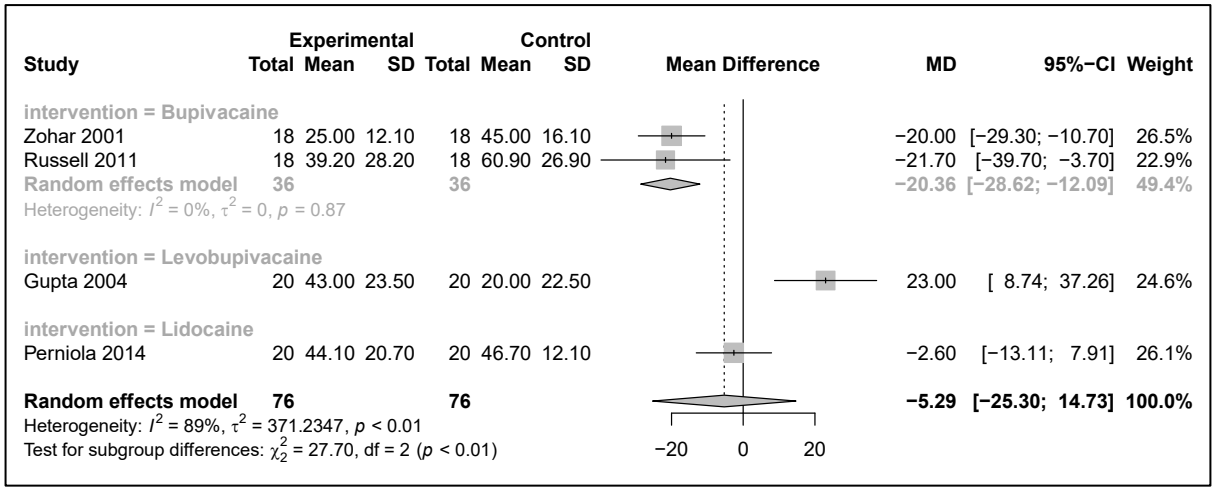

Figure 4. Difference in means for pain with movement on postoperative day one (measured 24 hours after surgery)

Pain intensities were reported using a 100-point scale, with 0 being no pain. Negative values indicate less pain at rest in the intervention group compared to the control/sham group. MD: Mean difference, 95%-CI: 95% confidence interval, df: degrees of freedom.

Postoperative opioid consumption on postoperative day one (24 hours)

Two studies reported data on opioid consumption rates in the 24 hour period following surgery (Gupta et al. 2004; Perniola et al. 2014; Figure 5). (19, 20) Both studies reported that opioid consumption was lower in their intervention group compared to the control/sham

group. The difference in point estimates between the two studies was large, differing by approximately 14 mg; Perniola et al (19) showed an effect larger than that of Gupta et al. Further, when examining the upper bound of the 95% CIs, only the study by Perniola and colleagues (19) showed that the data were consistent with a large effect size. The 95% CIs for both studies were wide, indicating a lack of precision of the estimates, thus weakening any conclusions that can be drawn from the data. The point estimate for the random effects model was -21.30 mg (in favour of the local anaesthetic group). This result was statistically significant. However, the range of plausible values was very wide (-34.78 to -7.83 mg) indicating that this result may be imprecise. There was no significant difference between the two subgroups (Levobupivacaine, Lidocaine).

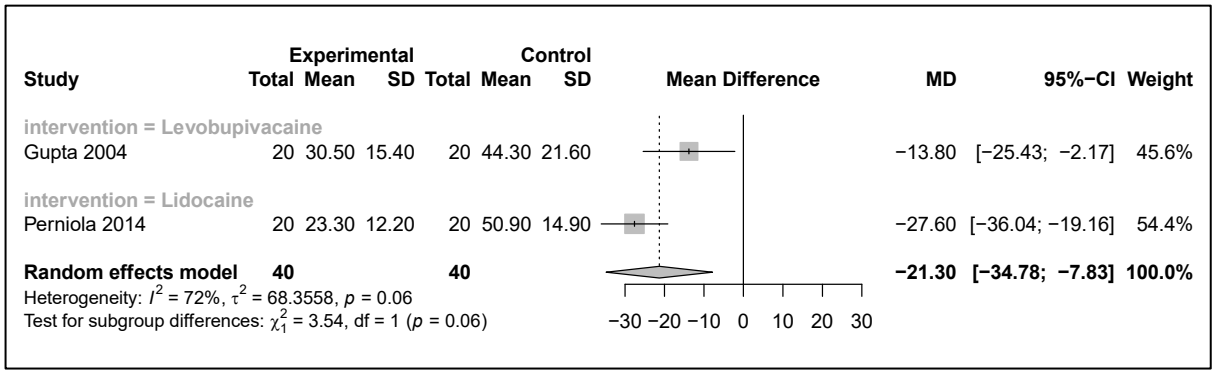

Figure 5. Difference in means for opioid consumption (mg of morphine equivalents) in the first 24 hours after surgery

Negative values indicate less opioid use in the intervention group compared to the control/sham group. MD: Mean difference, 95%-CI: 95% confidence interval, df: degrees of freedom.

Postoperative pain at rest after postoperative day one (after 24 hours)

No studies provided usable data for pain at rest in the 24 to 48 hour period following surgery.

Postoperative pain on movement after postoperative day one (after 24 hours)

No studies provided usable data for pain with movement in the 24 to 48 hour period following surgery.

Postoperative opioid consumption after postoperative day one (after 24 hours)

Two studies reported data on opioid consumption rates in the 24 to 48 hour period following surgery (Gupta et al. 2004; Perniola et al. 2014; Figure 6). One study (Gupta et al. 2004) reported a slight decrease in opioid consumption, while the other study (Perniola et al. 2014) reported a slight increase in consumption. (19, 20) In both cases the range of plausible values were wide, indicating lack of precision, and included zero difference in means between the intervention and the control/sham groups. The point estimate of the random effects model was 1.10 mg (in favour of the control group), but the estimate was very imprecise (-9.17 to 11.37 mg) and crossed the line of zero difference. The result is thus statistically insignificant. There was no significant difference between the two subgroups (Levobupivacaine, Lidocaine).

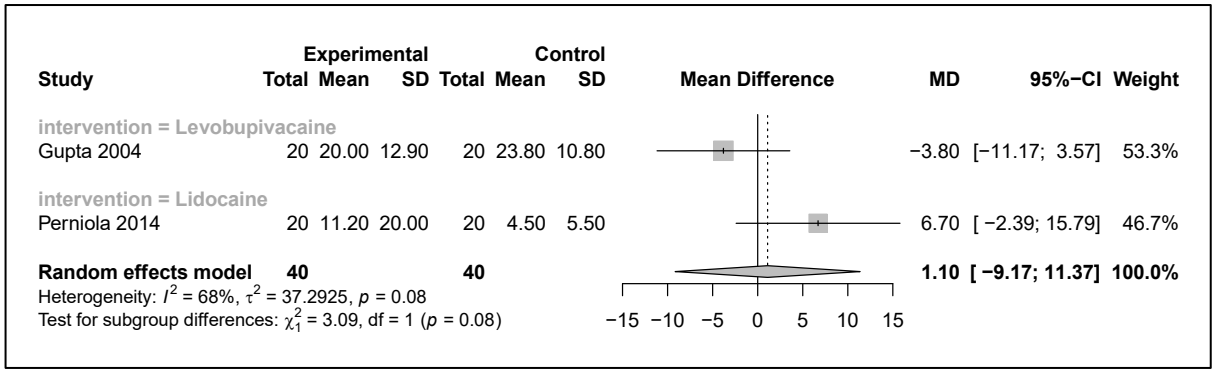

Figure 6. Difference in means for opioid consumption (mg of morphine equivalents) in the 24-48 hour period after surgery

Negative values indicate less opioid use in the intervention group compared to the control/sham group. MD: Mean difference, 95%-CI: 95% confidence interval, df: degrees of freedom.

Postoperative opioid related adverse events

Across the six studies, four types of opioid related adverse events were reported: nausea, vomiting, nausea or vomiting and pruritis.

Four of the six studies included in the review reported separately on nausea (Gupta et al. 2004; Marić et al. 2009; Perniola et al. 2014; Zohar et al. 2001) and/or vomiting (Gupta et al. 2004; Perniola et al. 2014), while one study (Russell et al. 2011) did not separate the two opioid side effects. (17, 19-21) In the study by Russell et al, (17) nausea or vomiting was more common in the control/sham group compared to the intervention group (44.4% vs 27.8%).

Table 2 evaluates the frequency of nausea across the four above mentioned studies. Across the four studies that reported on the frequency of nausea, three reported a lower frequency of the symptom in the intervention versus control/sham group (Gupta et al. 2004; Marić et al. 2009; Perniola et al. 2014), while one study reported a greater frequency of nausea in the intervention group compared to the control/sham group (Zohar et al. 2001); all patients in the intervention group reported having nausea. (17, 19-22) However, when examining the forest plot (Figure 7), it is clear that while the point estimates are consistent with lower odds of nausea in the intervention groups compared to control/sham these results are not statistically significant and are consistent with a small, imprecise effect. In the studies by Gupta et al and Marić et al, the upper bounds of the 95% CIs for two of the studies are consistent with a small effect (Gupta et al. 2004; Marić et al. 2009). (19-21) In the study by Zohar et al, (22) there was a substantial increase in the odds of nausea in the intervention group compared to the control/sham group, but the 95% CI was very wide indicating a serious lack of precision, which indicates that the finding is unreliable, making interpretation difficult.

Table 2. Frequency of nausea

	Intervention (%)	Control/sham (%)
Zohar et al. 2001	100	44
Gupta et al. 2004	15	50
Marić et al. 2009	18	44
Perniola et al. 2014	20	40

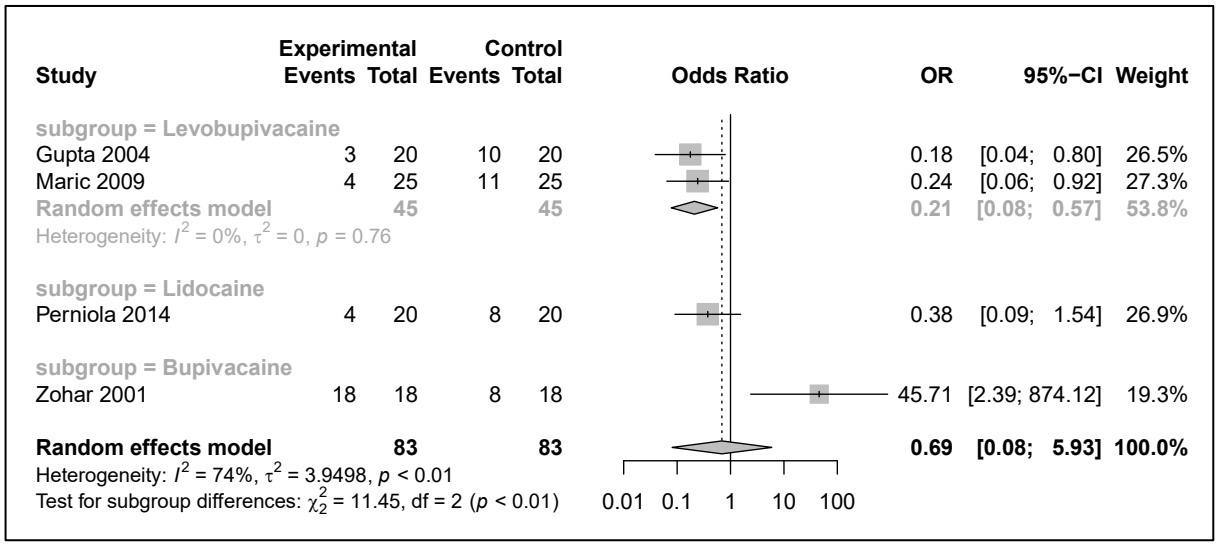

Figure 7. Odd ratios of nausea

Values less than one indicate that the odds of nausea were lower in the intervention group compared to the control/sham group. OR: Odds ratio, 95%-CI: 95% confidence interval, df: degrees of freedom

For the two studies that reported on the frequency of vomiting (Table 3), one reported an equal frequency of vomiting in the intervention and the control/sham group (Gupta et al. 2004), while the other reported a greater frequency of vomiting in the control/sham group compared to the intervention group (Perniola et al. 2014). (19, 20)

Figure 8 displays the forest plot for the odds ratio of vomiting. In both studies, the 95% CI for the estimate odds ratio were broad, indicating a lack of precision of the estimates. In the study by Gupta et al, (20) the point estimate of the odds ratio was 1, with a 95% CI that covered both a benefit and a harm in terms of vomiting. In the study by Perniola, (19) the point estimate indicated a strong reduction in the odds of vomiting in the intervention group compared to the control/sham group, but the upper limit of the 95% CI for the odds ratio was greater than 1, indicating that the data was consistent with no effect or even harm. This makes the overall lower odds ratio of vomiting in the intervention compared to control group unreliable and difficult to interpret. In addition, the overall lower odds ratio crosses the line of no effect and is thus insignificant.

Table 3. Frequency of vomiting

	Intervention (%)	Control/sham (%)
Gupta et al. 2004	10	10
Perniola et al. 2014	0	20

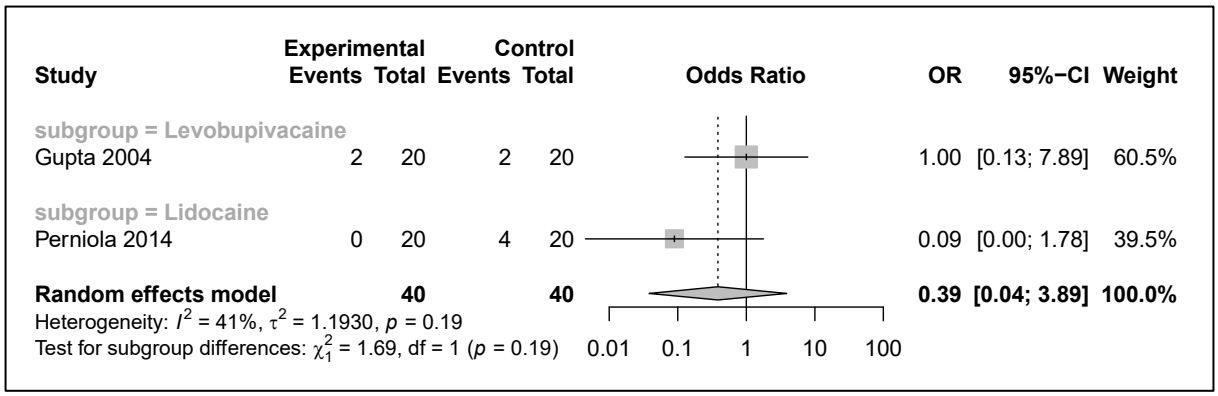

Figure 8. Odd ratios of vomiting

Values less than one indicate that the odds of vomiting were lower in the intervention group compared to the control/sham group. OR: Odds ratio, 95%-CI: 95% confidence interval

The incidence of pruritis was also evaluated as an opioid related adverse event. The study by Russel et al (17) assessed the incidence of pruritis in the intervention versus sham group. There was a higher incidence of pruritis in the sham group versus the intervention group

(55.6% vs 44.4%). As only a single study reported on this opioid related adverse event, the significance of this data could not be further statistically analysed in our meta-analysis.

Length of postoperative hospital stay

Two studies reported data on length of hospital stay (Gupta et al. 2004; Perniola et al. 2014). (19, 20) In both studies, the data was not analysed statistically, but there was no clear differences between the intervention and control/sham groups in either study (Table 4).

Table 4. Length of stay in hospital

	Intervention **[median (range) days]**	**Control/sham** **[median (range) days]**
Gupta et al. 2004	4 (2-6)	4 (2-11)
Perniola et al 2014	2 (2-3)	2 (2-3)

Major postoperative adverse events

Three studies reported on major postoperative adverse events. Two of these studies reported on local anaesthetic toxicity (Gupta et al. 2004; Perniola et al. 2014), with both studies showing no evidence of this event in both the intervention or control group. (19, 20) Wound infection was also specifically reported on by two studies as a major postoperative adverse event. The study by Kristensen et al (18) showed no evidence of wound infection in both the intervention and control group, whereas the study by Gupta et al (20) had one suspected case of wound infection in the control group (5%).

1.6 Discussion

1.6.1 Summary of evidence

This review compared the effectiveness of wound infusion of local anaesthetic versus placebo/sham for controlling postoperative pain after total abdominal hysterectomy. We identified six trials, contributing to a total of 244 patients to our systematic review and meta-analysis (Kristensen et al. 1999; Zohar et al. 2001; Gupta et al. 2004; Marić et al. 2009; Russel et al. 2011; Perniola et al. 2014). (17-22)

All six included trials, randomised participants to either wound infusion of a local anaesthetic or a placebo as a module of a multimodal analgesic regimen, in which all participants were given additional simple non-opioid analgesics as well as opioids to achieve adequate pain relief. All trials used numerical pain scores, which were converted to a 100mm VAS (0 = no pain; 10 to 30 = mild pain; 40 to 60 = moderate pain; 70 to 100 = severe pain) and opioid consumption to evaluate the analgesic efficacy of wound infusion of local anaesthetic versus placebo for pain management post abdominal hysterectomy.

Overall, our meta-analysis indicated that wound instillation of local anaesthetic post abdominal hysterectomy significantly reduced pain at rest and opioid consumption 24 hours post abdominal hysterectomy. As a result of the large amount of heterogeneity in this analysis, as well the effect sizes potentially being small and imprecise, these results need to be interpreted with caution and warrants further research.

The results of our meta-analysis also showed a decrease in pain on movement 24 hours post-surgery, however these results were not statistically significant. The small numbers of study participants, incomplete reporting of all outcomes across studies and heterogeneity of methods between studies may contribute to this. We also noted a disparity between treatment effects noted between pain scores and opioid consumption, highlighting the subjective nature of pain score reporting and its downfalls in measuring treatment effects.

The analysis also showed that the analgesic effect of continuous local anaesthetic wound infusion versus control or sham is probably not sustained, with no effect on opioid consumption after postoperative day one (24-48 hour period after surgery).

Recognised opioid related adverse events include nausea or vomiting, ileus, urinary retention, pruritus, sedation, respiratory depression or sleep disturbances. Four studies reported on the incidence of nausea, two studies on the incidence of vomiting, one study on the incidence of nausea or vomiting and one study on the incidence of pruritis. Most of the reported studies showed a reduction in the number of opioid related adverse events. However, our analysis found no evidence of a significant difference between the local anaesthetic group and the control group in the rates of postoperative opioid-related adverse events such as nausea, vomiting or pruritis. This may be due to a lack of power to detect small effect sizes, which is possibly compounded by the small number of study participants and imprecise nature of the data collected. Although our study showed a significant reduction in opioid consumption, this

may not necessarily parallel a significant reduction in opioid related adverse events, as opioid use is only one of a multitude of perioperative risk factors that contribute to these above-mentioned events. (10)

Length of hospital stay provides an indication of functional recovery after surgery and is a valuable marker of quality in healthcare system.(10) No clear differences between the length of hospital stay was noted between the intervention and control groups, in the two studies that reported on this outcome. The length of hospital stay could also be a valuable marker of cost effectiveness of an intervention, especially in resource limited settings.

This analysis reported no major adverse events associated with instillation of local anaesthetic post abdominal hysterectomy, therefore highlighting its safety profile in the management of pain after this procedure. The absence of complications related to an intervention is vitally important in resource constrained environments where there is a paucity of post-operative facilities, which is noted in most developing countries like ours.

The results of this review are in keeping with literature supporting local anaesthetic infusions post other types of abdominal surgery, however the strength of the recommendations from this analysis is much weaker due to the limitations noted in our study. In the study by Li et al (23) which assessed local anaesthetic infusion post caesarean section in 512 patients, it was found that intervention of local anaesthetic infusion was associated with significantly lower morphine consumption, lower rate of nausea but not with lower pain scores. Liang et al (10) assessed the effectiveness of continuous local anaesthetic after elective midline laparotomy for colorectal resection. Their study showed continuous wound infusion of a local anaesthetic compared to a normal saline placebo reduces postoperative pain at rest and the length of hospital stay, on the basis of high-certainty evidence.

In contrast to the above mentioned studies, a study by Kushner et al (24) found that their trial did not support the use of a bupivacaine wound infusion system for the management of postoperative pain in gynaecologic oncology procedures. This trial highlights that there is some conflicting literature regarding this pain management intervention, further emphasising the need for future high quality research.

1.6.2 Limitations

The six included trials had a small number of participants (total sample size range: 36 to 50). Small trials can produce imprecise overestimates of the true effect and may correlate with a higher risk of bias. (25-27) They are also more prone to the effects of random chance. (25, 26)

The implementation of local anaesthetic wound infusion varied across the included trials in factors such as the number, type and location of the wound catheter, the type of local anaesthetic agent, concentration and dose, the infusion programme (bolus vs continuous infusion), and the perioperative analgesic co-interventions or adjuncts used in the trials. This may account for the moderate to high levels of heterogeneity in the analyses in this review. This warrants further investigation through high-quality, randomised controlled trials which standardises the above mentioned factors.

Incomplete reporting of predefined objectives was present in all six included trials. All of our attempts to obtain the unpublished results were unsuccessful. We were required to estimate the mean and standard deviation of some outcomes from the median and range using various statistical methods. In some instances only a 95% CI was reported, and the standard deviation needed to be estimated from this using recommended statistical methods.

1.6.3 Future research

This study highlighted a number of areas to be addressed by further research. High quality, larger randomised controlled trials are necessary to evaluate the optimal implementation of local anaesthetic wound infusion post abdominal hysterectomy with regards to number and location of wound catheters, choice and dose of anaesthetic agent and continuous infusion versus bolus regimen programme. It may be prudent to standardise some of these factors in future trials to be able to thoroughly evaluate each of the above mentioned factors, to determine the most optimal treatment regime. Subgroup analyses of these trials may also allow one to further evaluate the efficacy of this intervention. Furthermore, comparing local anaesthetic infusion to alternate regional or neuraxial techniques such as plane blocks or epidurals, may provide useful practical information in the care of a patient post abdominal hysterectomy. Lastly, health economic evaluations of local anaesthetic wound infusion are merited to balance the cost of wound infusion devices against the economic benefits of potentially fewer adverse events, faster recovery and more costly alternatives.

1.6.4 Conclusions

In conclusion, this meta-analysis assessed the effectiveness of local anaesthetic infusion post abdominal hysterectomy in 244 patients across six RCTs. Local anaesthetic infusion was found to be effective in reducing pain at rest and opioid consumption 24 hours post abdominal hysterectomy and the intervention was free of complications across a group of heterogenous studies (compared to placebo). The intervention did not significantly reduce pain on movement 24 hours post-surgery. Larger high quality future studies are needed to evaluate the true efficacy of this intervention especially with regards to number and location of wound catheters, choice and dose of anaesthetic agent and continuous infusion versus bolus regimen programme.

1.7 Funding sources

No funding was required for this study

1.8 Conflicts of interest

The authors declare that they do not have any conflict of interest

1.9 Word Count

8371 words

1.9 References

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Supplementary Table 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	10
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	11
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	11
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	12
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	13
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	12
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	13

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	16
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	23
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	26

Supplementary table 2. List of search terms

Databases	Search terms
PubMed	1. ("Hysterectomy"[MeSH Terms] AND "anesthetics, local"[MeSH Terms]) 2. (hysterectomy) AND (local anaesthetics) 3. Search: #1 AND #2 4. ((hysterectomy) AND (local anaesthetics)) AND (postoperative pain) 5. ("Hysterectomy"[MeSH Terms] AND "anesthetics, local"[MeSH Terms] AND ("randomized controlled trial"[Publication Type] AND "humans"[MeSH Terms]) AND (("Hysterectomy"[MeSH Terms] OR "Hysterectomy"[All Fields] OR "hysterectomies"[All Fields]) AND ("local anaesthetics"[All Fields] OR "anesthetics local"[Pharmacological Action] OR "anesthetics, local"[MeSH Terms] OR ("anesthetics"[All Fields] AND "local"[All Fields]) OR "local anesthetics"[All Fields] OR ("local"[All Fields] AND "anesthetics"[All Fields])) AND ("randomized controlled trial"[Publication Type] AND "humans"[MeSH Terms])) AND ("randomized controlled trial"[Publication Type] AND "humans"[MeSH Terms]) AND (("Hysterectomy"[MeSH Terms] OR "Hysterectomy"[All Fields] OR "hysterectomies"[All Fields]) AND ("local anaesthetics"[All Fields] OR "anesthetics local"[Pharmacological Action] OR "anesthetics, local"[MeSH Terms] OR ("anesthetics"[All Fields] AND "local"[All Fields]) OR "local anesthetics"[All Fields] OR ("local"[All Fields] AND "anesthetics"[All Fields])) AND ("pain, postoperative"[MeSH Terms] OR ("pain"[All Fields] AND "postoperative"[All Fields]) OR "postoperative pain"[All Fields] OR ("postoperative"[All Fields] AND "pain"[All Fields])) AND ("randomized controlled trial"[Publication Type] AND "humans"[MeSH Terms]))) AND ((randomizedcontrolledtrial[Filter]) AND (humans[Filter]))

	6. (((((((hysterectomy) AND (local anaesthetic infusion)) OR (local anaesthetic infiltration)) OR (wound catheter infusion)) OR (local anaesthetic)) OR (wound infiltration)) OR (wound infusion)) OR (continuous local anaesthetic wound infusion)) OR (elastomeric balloon pump) 7. #5 AND #6 8. (hysterectomy) AND (continuous local anaesthetic infusion) 9. #7 AND #8 10. (hysterectomy) AND (wound catheter) 11. #9AND #10
Web of Science	1. (ALL=(hysterectomy)) AND ALL=(local anaesthetics) 2. ((ALL=(hysterectomy)) AND ALL=(local anaesthetics)) AND ALL=(postoperative pain) 3. #1 AND #2 4. (((((((ALL=(hysterectomy)) AND ALL=(local anaesthetic infusion)) OR ALL=(local anaesthetic infiltration)) OR ALL=(wound catheter infusion)) OR ALL=(local anaesthetic)) OR ALL=(wound infiltration)) OR ALL=(wound infusion)) OR ALL=(continuous local anaesthetic wound infusion) 5. #3 AND #4 6. (ALL=(hysterectomy)) AND ALL=(continuous local anaesthetic infusion) 7. #5 AND #6

	8. (ALL=(hysterectomy)) AND ALL=(wound catheter) 9. #7 AND #8
MEDLINE complete	1. MH "Hysterectomy") AND (MH "Anesthetics, Local") 2. hysterectomy AND local anesthetics 3. (hysterectomy AND local anesthetics) AND (S1 AND S2) 4. hysterectomy AND local anesthetics AND postoperative pain 1. S3 AND S4 6. hysterectomy AND local anaesthetic infusion OR local anaesthetic infiltration OR wound catheter infusion OR local anaesthetic OR wound infiltration OR wound infusion OR continuous local anaesthetic wound infusion OR elastomeric balloon pump 7. hysterectomy AND local anaesthetic infusion OR local anaesthetic infiltration OR wound catheter infusion OR local anaesthetic OR wound infiltration OR wound infusion OR continuous local anaesthetic wound infusion OR elastomeric balloon pump) AND (S5 AND S6) 8. hysterectomy AND continuous local anaesthetic infusion 9. (hysterectomy AND continuous local anaesthetic infusion) AND (S7 AND S8) 10. hysterectomy AND wound catheter 11. S9 AND S10
SCOPUS	1. (TITLE-ABS-KEY (hysterectomy) AND TITLE-ABS-KEY (local AND anaesthetics))

	2. (TITLE-ABS-KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetics) AND TITLE-ABS- KEY (postoperative AND pain)) 3. ((TITLE-ABS-KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetics) AND TITLE-ABS- KEY (postoperativeAND pain))) AND ((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetics))) 4. (TITLE-ABS-KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetic AND infusion) OR TITLE-ABS- KEY (localAND anaesthetic AND infiltration) OR TITLE-ABS- KEY (wound AND catheter AND infusion) OR TITLE-ABS- KEY (localAND anaesthetic) OR TITLE-ABS- KEY (wound AND infiltration) OR TITLE-ABS- KEY (wound AND infusion) OR TITLE-ABS- KEY (continuous AND local AND anaesthetic AND wound AND infusion) OR TITLE-ABS-KEY (elastomeric ANDballoon AND pump)) 5. (((TITLE-ABS-KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetics) AND TITLE-ABS- KEY (postoperative AND pain))) AND ((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetics)))) AND ((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (local ANDanaesthetic AND infusion) OR TITLE-ABS- KEY (local AND anaesthetic AND infiltration) OR TITLE-ABS- KEY (wound AND catheter AND infusion) ORTITLE-ABS- KEY (local AND anaesthetic) OR TITLE-ABS- KEY (wound AND infiltration) OR TITLE-ABS- KEY (wound AND infusion) OR TITLE-ABS- KEY(continuous AND local AND anaesthetic AND wound AND infusion) OR TITLE-ABS-KEY (elastomeric AND balloon AND pump)))

	6. (TITLE-ABS-KEY (hysterectomy) AND TITLE-ABS- KEY (continuous AND local AND anaesthetic AND infusion)) 7. ((((TITLE-ABS-KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetics))) AND ((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetics) AND TITLE-ABS- KEY (postoperative AND pain)))) AND ((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (local ANDanaesthetic AND infusion) OR TITLE-ABS- KEY (local AND anaesthetic AND infiltration) OR TITLE-ABS- KEY (wound AND catheter AND infusion) ORTITLE-ABS- KEY (local AND anaesthetic) OR TITLE-ABS- KEY (wound AND infiltration) OR TITLE-ABS- KEY (wound AND infusion) OR TITLE-ABS- KEY (continuous AND local AND anaesthetic AND wound AND infusion) OR TITLE-ABS- KEY (elastomeric AND balloon AND pump)))) AND ((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (continuous AND local AND anaesthetic AND infusion))) 8. (TITLE-ABS-KEY (hysterectomy) AND TITLE-ABS- KEY (wound AND catheter)) 9. ((TITLE-ABS-KEY (hysterectomy) AND TITLE-ABS- KEY (wound AND catheter))) AND (((((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetics))) AND ((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetics) AND TITLE-ABS- KEY (postoperativeAND pain)))) AND ((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (local AND anaesthetic AND infusion) OR TITLE-ABS- KEY (local ANDanaesthetic AND infiltration) OR TITLE-ABS- KEY (wound AND catheter AND infusion) OR TITLE-ABS-

	KEY (local AND anaesthetic) OR TITLE-ABS- KEY(wound AND infiltration) OR TITLE-ABS- KEY (wound AND infusion) OR TITLE-ABS- KEY (continuous AND local AND anaesthetic AND wound ANDinfusion) OR TITLE-ABS- KEY (elastomeric AND balloon AND pump)))) AND ((TITLE-ABS- KEY (hysterectomy) AND TITLE-ABS- KEY (continuousAND local AND anaesthetic AND infusion))))
Cochrane Library	1. MeSH descriptor: [Hysterectomy] explode all trees AND MeSH descriptor: [Anesthetics, Local] explode all trees 2. ("hysterectomy"):ti,ab,kw AND ("local anaesthetics"):ti,ab,kw 3. #1 AND #2 4. ("hysterectomy"):ti,ab,kw AND ("local anaesthetics"):ti,ab,kw AND ("postoperative pain"):ti,ab,kw 5. #3 AND #4 6. ("hysterectomy"):ti,ab,kw AND (local anaesthetic infusion):ti,ab,kw OR (local anaesthetic infiltration):ti,ab,kw OR (wound catheter infusion):ti,ab,kw OR (local anaesthetic):ti,ab,kw OR (wound infusion):ti,ab,kw OR (continuous local anaesthetic wound infusion):ti,ab,kw OR (elastomeric balloon pump):ti,ab,kw 7. (“hysterectomy"):ti,ab,kw AND (local anaesthetic infusion):ti,ab,kw OR (local anaesthetic infiltration):ti,ab,kw OR (wound catheter infusion):ti,ab,kw OR (local anaesthetic):ti,ab,kw OR (wound infusion):ti,ab,kw OR (continuous local anaesthetic wound infusion):ti,ab,kw OR (elastomeric balloon pump):ti,ab,kw AND 5 8. ("hysterectomy"):ti,ab,kw AND (continuous local anaesthetic infusion):ti,ab,kw

	9. #7 AND #8 10. ("hysterectomy"):ti,ab,kw AND (wound catheter):ti,ab,kw 11. #9 AND #10
OVID	1. (hysterectomy and local anaesthetics).af. 2. hysterectomy and local anaesthetics and postoperative pain).af. 3. 1 and 2 4. ((hysterectomy and local anaesthetic infusion) or local anaesthetic infiltration or wound catheter infusion or local anaesthetic or wound infiltration or wound infusion or continuous local anaesthetic wound infusion or elastomeric balloon pump).af. 5. 3 and 4 2. hysterectomy and continuous local anaesthetic infusion).af. 3. 5 and 6 4. (hysterectomy and wound catheter).af. 5. 7 and 8

Supplementary table 3. JBI revised critical appraisal tool for assessment of risk of bias for RCTs

RoB assessor:		Date of appraisal:	Record number:			
Study author:		Study title:	Study year:			
Internal validity		Choice - comments/ justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	Was true randomization used for assignment of participants to treatment groups?		☐	☐	☐	☐
2	Was allocation to treatment groups concealed?		☐	☐	☐	☐
3	Were treatment groups similar at the baseline?		☐	☐	☐	☐
Bias related to administration of intervention/exposure						
4	Were participants blind to treatment assignment?		☐	☐	☐	☐
5	Were those delivering the treatment blind to treatment assignment?		☐	☐	☐	☐
6	Were treatment groups treated identically other than the intervention of interest?		☐	☐	☐	☐
Bias related to assessment, detection, and measurement of the outcome						
7	Were outcome assessors blind to treatment assignment?		Yes	No	Unclear	N/A
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐
8	Were outcomes measured in the same way for treatment groups?		Yes	No	Unclear	N/A
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐
9	Were outcomes measured in a reliable way?		Yes	No	Unclear	N/A
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

Statistical conclusion validity		Choice - comments/ justification	Yes	No	Unclear	N/A
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 4		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 5		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 6		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 7		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
12	Was appropriate statistical analysis used?					
	Outcome 1		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 4		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 5		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 6		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Statistical conclusion validity		Choice - comments/ justification	Yes	No	Unclear	N/A
	Outcome 7		Yes	No	Unclear	N/A
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
13	Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?		☐	☐	☐	☐
Overall appraisal:	**Include:** ☐	**Exclude:** ☐	**Seek further info:** ☐			
Comments:						

Supplementary table 4. Evaluation of data availability for primary and secondary objectives

Objective	Data availability					
	Kristensen *et al.*	Zohar *et al.*	Gupta *et al.*	Marić *et al.*	Russell *et al.*	Perniola *et al.*
Postoperative pain at rest postoperative day 1 (at 24 hours)						
Postoperative pain on movement postoperative day 1 (at 24 hours)						
Postoperative opioid consumption on postoperative day 1	1					
Postoperative pain at rest after postoperative day 1						
Postoperative pain on movement after postoperative day 1						
Postoperative opioid consumption after postoperative day 1 (24-48 hours)						
Postoperative opioid-related adverse events (nausea and/or vomiting at 24 hours)						
Major postoperative adverse events						
Length of postoperative hospital stay						

Supplementary table 4. Evaluation of data availability for primary and secondary objectives

Data availability for each objective. Green indicate that usable data available, yellow indicate that incomplete data provided (1: mean data only, with no measure of precision or variance), grey indicates that the data was not reported

Appendix 1. Proposal

Local anaesthetic wound infusion for postoperative pain management following an abdominal hysterectomy: A systematic review

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1. Introduction/Background

A hysterectomy is defined as the surgical removal of the uterus. Hysterectomies are the most commonly performed major surgical procedure in women worldwide. In the United States of America, more than 500 000 hysterectomies are performed annually(28). Data around hysterectomies in South Africa are scarce, particularly with regard to the number of cases performed each year. However, audits of healthcare institutions' surgical registers and publication of data regarding clinical aspects of hysterectomies suggest that, in line with international data, hysterectomies are also one of the most commonly performed surgical procedures in women in South Africa.

A hysterectomy can be can be performed for a number of gynaecological indications. Some of these include abnormal uterine bleeding, leiomyomas, chronic pelvic pain, uterine prolapse, malignant or premalignant conditions and gender reassignment surgery. An audit done by a tertiary hospital in South Africa revealed that the most common indication for hysterectomy was menorrhagia due to fibroids (23%), followed by abnormal uterine bleeding of undetermined origin (14.9%), endometrial cancer (13.4%), uterine prolapse (11.3%) and cervical cancer (10.7%) (4).

Surgical approaches to a hysterectomy can be categorised into four options: abdominal hysterectomy (AH), vaginal hysterectomy, laparoscopic hysterectomy and robotic assisted hysterectomy. A total hysterectomy refers to the entire removal of the uterus and cervix; if the cervix is not removed, the procedure is classified as a subtotal or supracervical hysterectomy. Each approach has myriad of pros and cons. An abdominal hysterectomy is more invasive, causes greater postoperative pain and results in longer recovery times. Less invasive approaches provide benefits in terms of pain, earlier mobilisation and quicker recovery. A meta-analysis done by Aarts et al (29) revealed that a vaginal hysterectomy is superior to abdominal and laparoscopic approaches, with earlier recovery and a lower rate of complications. The study highlighted that where a vaginal hysterectomy was not feasible, either an abdominal or laparoscopic approach could be considered. More frequently, hysterectomies are being done with minimally invasive approaches to reduce postoperative pain, reduce the length of hospital stay, decrease recovery times and improve patient satisfaction. However, there are still many clinical indications that necessitate an abdominal approach.

The type of hysterectomy performed depends on the patient's clinical picture, the expertise of the surgeon and the surgical amenities available. The patient's clinical considerations that influence this decision include: the condition being treated, their body habitus, physiological status and the size of the uterus. The abdominal approach is indicated in most emergencies as well as in patients with malignancies and those with large leiomyomas (30). The most recent audit done by Butt et al (4) showed that the abdominal approach is still the most common surgical approach in South Africa (65.1%).

An abdominal hysterectomy can either be performed via Pfannestial incision or less commonly, a midline incision. Both of these methods require dissecting through several layers of the abdominal wall to gain access to the deep pelvic cavity. These layers include: skin, subcutaneous tissue, fascia, the rectus sheath and the visceral and parietal peritoneum. Once in the pelvic cavity, a deep pelvic dissection is done. This procedure leads to significant tissue damage as the layers are traversed. An abdominal hysterectomy results in both visceral and somatic pain. Visceral pain arises from the autonomic innervation of the parametrium, upper vagina and visceral peritoneum. The somatic component of pain arises from the skin, fascia, muscle and subcutaneous tissue that is transected (31).

An abdominal hysterectomy is associated with moderate to severe postoperative pain (32). Normal physiological pain is caused by activation of nociceptors in skin, muscle, connective tissue and viscera. Tissue damage during surgery acts as an intense, noxious mechanical, chemical and/or thermal stimulus that activates nociceptors (33). Nociceptors provide sensory input to the dorsal horn of the spinal cord. In the spinal cord, contact is made with second order neurons which decussate. Pain impulses ascend in the contralateral spinothalamic tract, passing through the thalamus and reticular activating system, to reach the somatosensory cortex. The perception of pain occurs at the level of the somatosensory cortex. Various pharmacological agents can interfere with this transmission of the pain impulse by interrupting impulse transmission along the pathway, to reduce the perception of pain (28).

Postoperative pain control is a challenging aspect of both surgical and anaesthetic management. Effective post-operative pain management has been shown to improve patient comfort and satisfaction, as well as to promote earlier mobilisation leading to faster recovery and reduced cost of care. Tsui et al (8) demonstrated that adequate postoperative analgesia has been associated with a decreased incidence of cardiopulmonary complications, hospital

mortality, hospital stay and hospital cost. Patients' satisfaction and subjective success of an operation are also significantly influenced by the efficacy of analgesia both in the acute postoperative period and long term period following surgery(34).

Emerging clinical evidence has shown that poorly managed acute postoperative pain can lead to the development of chronic pain. Chronic pain is defined as pain persisting for more than 3 months after surgery. Chronic pain results in a poor quality of life and places a significant burden on healthcare systems and social support structures (35). It is important to prevent the development of chronic pain, and therefore, managing acute post-operative pain adequately is of great preventative benefit.

Chronic pain after a hysterectomy is fairly common. In a recent study done by Beyaz et al (6), approximately 30% of patients developed chronic pain after undergoing a hysterectomy. Other literature supports these statistics with the prevalence of chronic pain quoted as being 5-32%. Female gender and the presence of preoperative pain are additional risk factors for the development of chronic pain, placing women who undergo hysterectomy at an even higher risk for the development of chronic pain (33).

Owing to the complex nature of the pain associated with hysterectomies, several different modalities of pain management have been employed. These include, but are not limited to, multimodal analgesia techniques, epidural analgesia, intrathecal analgesia, local anaesthetic infiltration, patient controlled analgesia (PCA) pumps, regional nerve blocks or plane blocks and pre-emptive analgesia techniques (28). Less commonly used non-pharmacological techniques include music therapy, acupuncture and hypnotherapy. Multimodal analgesia combines analgesic drugs from different classes which employ different mechanisms of action to reduce the sensation of pain. The use of different drug classes has a synergistic effect which maximizes pain relief at lower analgesic doses, whilst reducing the risk of adverse drug effects (36). Examples of these drugs include opioids, non-steroidal anti-inflammatory drugs (NSAIDS), selective cyclooxygenase-2 (COX-2) inhibitors, paracetamol, N-methyl-D-aspartate (NMDA) receptor antagonists and alpha 2 agonists.

There is a lack of current, high quality evidence assessing the use of different analgesic modalities individually or in combination. This leads to difficulty in formulating updated guidelines for optimal pain management. The most recent systematic review by Azari et al (28) in 2013, which assessed optimal pain management strategies for hysterectomies made the

following recommendations: The study advocated for the use of strong opioids in the intra-operative and post-operative period. The use of a morphine PCA was found to be highly effective and was the most common modality of opioid use. Paracetamol, gabapentin and NSAIDS used either in the pre-operative period as part of pre-emptive analgesia or used postoperatively, were also highly effective in reducing postoperative pain and are strongly advised to be included in the analgesic regimen. Epidural anaesthesia was found to have a limited effect both intraoperatively and postoperatively, however intrathecal morphine may have a useful role. Lastly, with regards to local anaesthetics, once-off local anaesthetic infiltration was found to be ineffective due to its short duration of action. A transversus abdominis plane (TAP) block, however, was found to be useful and should be considered in selected patients. This review also noted that continuous local anaesthetic infusion of 0.25% bupivacaine above the abdominal fascia, via a wound catheter postoperatively, was effective in reducing postoperative pain.

PROSPECT (Procedure Specific Postoperative Pain Management) is group of anaesthesiologists and surgeons who have collaborated to develop a clinical decision support service regarding pain management. The aim of this committee is to improve postoperative pain management on a procedure-specific basis, by using evidence based research methodology, to formulate procedure-specific pain management guidelines. PROSPECT guidelines regarding abdominal hysterectomy were last formulated and updated in 2006; the following recommendations were made: Preoperatively, pre-emptive systemic analgesics were recommended, as was single shot spinal anaesthesia. Epidural analgesia should be considered in patients at high risk of developing severe postoperative pain. Intraoperatively, the use of strong opioids, local anaesthetic wound infiltration and continuous infusion of bupivacaine above the abdominal fascia was recommended. Postoperatively, a multimodal analgesia regimen consisting of strong and weak opioids, NSAIDS, COX-2 inhibitors and paracetamol, with appropriate stepdown as pain decreases, was advised. For patients who are at high risk of developing severe postoperative pain, epidural analgesia in the postoperative period was advocated (37).

Regarding continuous local anaesthetic infiltration, only pre-closure continuous infusion was found to be effective in the intraoperative period. In summary, PROSPECT recommends the use of a multimodal regimen and suggests that high risk patients may benefit from regional anaesthesia techniques (37).

There remains contrasting evidence regarding the most effective modalities for managing pain post abdominal hysterectomy. This contrast is particularly evident with regard to the effectiveness of local anaesthetic wound infusions. The use opioids throughout the perioperative period is key. There is, however, a paucity of high quality evidence in the literature which speaks to analgesic modalities that complement or reduce the needs for opioids post hysterectomy.

Opioids represent a class of centrally acting analgesics that provide powerful dose-dependent pain relief for moderate to severe pain. They are an exceedingly common analgesic tool for the clinician due to their affordability and effectiveness. Opioids effectively reduce pain originating from both visceral and somatic stimuli, as well pain that is neuropathic in origin. However, they can result in some undesirable effects, including respiratory depression, sleep disordered breathing, nausea, vomiting, constipation, urinary retention, pruritis, drowsiness, dependence, psychological disturbances and immunosuppression (38, 39). These can lead to increased morbidity in the postoperative period. Furthermore, exposure to opioids for even short periods of time can lead to development of opioid induced hyperalgesia, which can predispose to the development of chronic pain (40). It has been shown that patients who experience these adverse effects are likely to incur higher hospital costs and have prolonged hospital stays; they are also at increased risk of requiring reoperation (41). Consequently, there is a need to develop opioid-sparing and opioid-free analgesic techniques (42).

Enhanced recovery after surgery (ERAS) is a patient-centred, evidence-based, multimodal perioperative care pathway that aims to reduce the patient's physiological stress response to surgery, optimise their physiological function and facilitate earlier recovery (43). ERAS places emphasis on decreasing perioperative stress, resuming gastrointestinal function, achieving satisfactory pain control and early mobilisation. Effective analgesia is a key component. Strategies employed by ERAS include the use of non-opioid analgesics and early mobilisation, which is dependent on good quality postoperative analgesia. Postoperative pain is a significant barrier to early discharge in gynaecological surgery patients (44). ERAS programmes have had a positive impact on outcomes in gynaecological surgery by advocating the use of regional anaesthesia and limiting the use of strong opioids. A study done by Acka et al (44) showed that ERAS protocols in the setting of abdominal hysterectomy reduced the length of hospitals stays, improved patients' mental and physical wellbeing and quality of life one month after surgery.

Epidural or intrathecal analgesia can be considered the gold standard in treating pain post abdominal surgery. However, these techniques require expertise, postoperative monitoring and may have adverse effects especially in older patients. There has been recent interest in alternative methods for analgesia with minimal side-effects and a trend towards movement from central neuraxial blocks towards peripheral and less invasive techniques. Once such approach is local anaesthetic wound infusion (45).

Local anaesthetic agents are widely used for the provision of anaesthesia and analgesia throughout the perioperative period. A local anaesthetic can be defined as a drug which reversibly interrupts the transmission of a nerve impulse in the region in which it is applied, without affecting consciousness (7). These drugs are a heterogenous group of pharmacological agents that block voltage gated sodium channels. In normal neuronal tissue, noxious stimuli lead to activation of sodium channels causing sodium influx into the cell. This leads to the depolarisation of the neuronal cell, propagation of action potentials, and the subsequent transmission of a pain impulse (46). Local anaesthetic agents thus interrupt pain impulse transmission early in the pain pathway.

Many studies have shown that local anaesthetic wound infiltration or infusion is a useful adjunct in postoperative pain management (21, 24). The infiltration of surgical wounds with local anaesthetics has been widely practiced. The unwanted effects of opioids can be negated or reduced by the use of local anaesthetic agents(47). Due to their excellent analgesic profile and lack of opioid induced adverse effects, local anaesthetic drugs have become increasingly popular in treating pain (22). Their relatively low cost and safety profile make these agents appealing. Local anaesthetics have been shown to be bacteriostatic, immunomodulatory and can reduce the risk of tumour cell progression, which confers an additional benefit to patients presenting for abdominal hysterectomy due to malignancy (46, 48, 49).

Local anaesthetics can be infiltrated subcutaneously, injected intraperitoneally and infused intraabdominally with varying effectiveness (50). Single shot postoperative subcutaneous infiltration is widely practiced. When injected as a single dose, the analgesic effect of these agents lasts two to four hours (32). This short duration of action and the need for repeated administration, can be viewed as a hinderance of these agents (51).

Wound infusion with a solution of local anaesthetic was first described in 1953 (52). This practice evolved from the infusion of local anaesthetics through simple catheters that were

inserted prior to wound closure, to the development of special multi-holed wound catheters that can deliver an analgesic solution according to a pre-programmed regimen(47).
Wound catheter infusion kits are composed of the catheter, a closed-end thin hollow tube with side holes and the infusion device which can either be an elastomeric balloon pump or an electronic pump. The catheter is placed either in or alongside a surgical wound before closure and a local anaesthetic solution can be administered continuously or repeatedly into the wound. These catheters can be placed in the sub-peritoneal, pre-peritoneal or subcutaneous layer following abdominal surgery. The infusion device allows the controlled infusion of a local anaesthetic solution, either as a continuous programmed infusion rate or an intermittent bolus regimen into the surgical wound. After a few days, the catheter can be removed through a minimally invasive approach (9).

Continuous wound infusion allows the direct and sustained action of local anaesthetics within tissues surrounding a surgical wound, inhibiting nociception(10) The short duration of action of local anaesthetics, which previously hindered the widespread use of them as an effective postoperative analgesic modality has been negated. Wound infusion kits are simple to use, require little expertise, confer all the additional benefit of local anaesthetics and have a minimal adverse event profile.

Despite the obvious benefits and appeal of this modality, evidence is lacking regarding its use in gynaecological surgery.

The use of local anaesthetic wound infusions for alleviating postoperative pain has been studied in the past decade with conflicting reports. Clinicians hold distinctly different views with regards to the use of this technique. Two major endpoints to assess the efficacy of local anaesthetic wound infusion is 1) the reduction in opioid consumption and 2) the reduction in reported pain scores. A systematic review by Xiangan et al (53) assessed the use of local anaesthetic wound infusion in 512 patients post Caesarean section. The study showed that the technique was associated with significantly lower morphine consumption, lower rates of postoperative nausea, but not with lower pain scores compared to the placebo group. As Caesarean delivery and abdominal hysterectomy are both performed through a Pfannestial incision, they are both likely to have a similar somatic components of pain. However, an abdominal hysterectomy is associated with much more extensive tissue damage, making it difficult to directly extrapolate these results to pain management post hysterectomy.

Abdominal hysterectomy is an ideally suited surgery to assess the efficacy of local anaesthetic wound infusion for postoperative pain management following a major gynaecological surgery (22).

The use of local anaesthetic wound infusions have shown to be effective in providing pain relief and reducing analgesic requirements after a variety of abdominal surgery, including cholecystectomy and herniorrhaphy. However, there is some conflicting research which has also shown a lack of efficacy, which may have resulted in the limited utilisation of this technique (31, 47). A large systematic review assessing the effectiveness of continuous local anaesthetic wound infusion following colorectal surgery through a laparotomy, provided high certainty evidence showing that it reduces postoperative pain at rest and length of hospital stay. It also provided moderate certainty evidence that the technique reduced opioid consumption and time to first bowel movement(10). Colorectal surgery via laparotomy and hysterectomies are both major surgeries, suggesting the need to investigate the effectiveness of this technique for hysterectomies as well.

A study done by Mungroop et al. (54) highlighted that continuous preperitoneal infusion of local anaesthetic was as effective as epidural analgesia in treating pain post abdominal surgery, and could be favoured based on better recovery parameters and patient satisfaction. Complications associated with continuous local anaesthetic wound infusions are rarely reported in the literature. Some of these include delayed wound healing, increased risk of infections, haematoma and systemic toxicity. Coupled with its positive findings, further streamlined research to assess the usefulness of this intervention is warranted.

Several smaller randomised controlled trials have assessed the efficacy of this technique post abdominal hysterectomy. In keeping with the findings in other abdominal surgeries, the results have been conflicting. Some trials showed that local anaesthetic wound infusion reduced opioid consumption and pain scores (21, 51, 55, 56). Other trials showed evidence of improved patient satisfaction, reduced nausea and faster recovery of bowel function (21, 22). However Kristensen et al. (47) and Kushner et al. (31) revealed no differences in opioid consumption or pain scores at rest or with movement.

In summary, abdominal hysterectomies are commonly performed surgical procedures associated with moderate to severe postoperative pain. With the trend towards developing pain management strategies that are in line with ERAS protocols, and the need to minimise

opioid use, local anaesthetic wound infusion offers a simple, safe, low cost solution to improving pain management post hysterectomy. At present, the current data available supporting local anaesthetic wound infusion post hysterectomy is conflicting. This prevents clinicians from making an evidence based decision regarding this pain management modality. Previous systematic reviews looking at the effectiveness of local anaesthetic wound infusions have included a broad range of surgeries including gastrointestinal surgery, obstetric, gynaecological, urological, cardiothoracic and orthopaedic surgery (8). The validity and relevance of pooling outcomes from different surgical procedures can be viewed as questionable, as different surgical procedures cause pain by differing mechanisms, and as a result, present with differing pain intensities. The placebo and treatment responses also differ between different surgical procedures and surgical incisions (57).

There is increasing recognition of the need for evidence based guidelines for procedure-specific pain management . At present, there is no systematic review examining the procedure specific outcomes of local anaesthetic wound infusion after abdominal hysterectomy.
The aim of my study is to critically review and appraise the literature available, regarding the effectiveness of local anaesthetic wound infusion for postoperative pain management following an abdominal hysterectomy, through the process of a systematic review.

2. Problem statement

Hysterectomies are one of the most commonly performed major surgical procedures in women worldwide. It is associated with moderate to severe postoperative pain. Poorly managed postoperative pain can lead to a number of adverse events, as well as to the development of chronic pain syndromes. Current pain management guidelines are centred around the use of strong opioids throughout the perioperative period. Opioid use has a number of adverse effects and can result in a delayed return to normal physiological function postoperatively. There is a paucity of evidence in the literature regarding pain management modalities that complement or reduce the need for strong opioids post abdominal hysterectomy, as well as those that improve overall postoperative pain management following a hysterectomy. Current literature shows conflicting data regarding the effectiveness of local anaesthetic wound infusions for postoperative pain management following hysterectomy.

3. Aim

To evaluate the effectiveness of local anaesthetic wound infusions through a wound catheter for postoperative pain management following an abdominal hysterectomy, by means of a systematic review.

4. Objectives

The **primary objectives** of this study are to determine the effect of local anaesthetic wound infusion on:

- Postoperative pain at rest and on movement on postoperative day 1 (24 hours)
- Postoperative opioid consumption on postoperative day 1 (24 hours)

(in comparison to placebo or sham)

The **secondary objectives** of this study are to determine the effects of local anaesthetic wound infusion on:

- Postoperative pain at rest and on movement **after** postoperative day 1 (**after** 24 hours)
- Postoperative opioid consumption **after** postoperative day 1 (**after** 24 hours)
- Postoperative opioid related adverse events
- Length of postoperative hospital stay
- Major postoperative adverse events

(in comparison to placebo or sham)

5. Research assumptions

The following research definitions or assumptions will be used in the study:

Hysterectomy: the surgical removal of the uterus, either completely or partially.

Abdominal hysterectomy: the surgical removal of the uterus through an incision in the lower abdomen.

Total abdominal hysterectomy: the removal of the uterus and cervix through an incision in the abdomen.

Subtotal hysterectomy: the partial removal of the uterus, where the cervix is not removed.

Local anaesthetic: a drug which reversibly interrupts the transmission of a nerve impulse in the region in which it is applied, through blockade of voltage gated sodium channels, without affecting consciousness.

Local anaesthetic wound infusion: the introduction of local anaesthetic through a catheter, embedded in or near a surgical wound, either continuously by infusion or repeatedly as bolus doses.

Wound catheter: a specially designed, closed end, multi-holed device, that is embedded in or near a surgical wound, to allow the repeated or continuous delivery of local anaesthetic or analgesic substances into the surgical site.

Placebo: an inactive substance that is used as a control, to compare results with an active substance, as part of a research undertaking. In this study, infusion of normal saline will be regarded as the placebo.

Sham: an inactive treatment or procedure that is intended to mimic a therapy in a clinical trial as closely as possible. It is essentially a faked medical intervention that omits a step thought to be therapeutically necessary. In this study, placement of wound catheter like device under a surgical dressing to mimic a wound catheter will be regarded as the sham. It will not be embedded in the wound nor will it allow for the administration of any substance.

Postoperative day 1: will be defined as one day (24 hours) after the surgical procedure.

Postoperative pain: will expressed as 10-point numerical rating scale or equivalent.

Postoperative opioid consumption: the cumulative opioid consumption in a predefined period, expressed as milligrams of morphine-equivalent opioid dose.

Postoperative opioid related adverse events: includes nausea or vomiting, ileus, urinary retention, pruritus, sedation, respiratory depression, sleep disturbance, or other opioid-related adverse events reported by trial authors.

Length of hospital stay: the time between completion of the surgery and time of discharge from hospital.

Major postoperative adverse events: includes death due to any cause after surgery, adverse events that result in death, are life-threatening, require prolongation of hospital stay or that result in a persistent or severe disability. These include: pulmonary complications (atelectasis, pneumonia, respiratory failure), venous thromboembolic complications (deep vein thrombosis, pulmonary embolism), wound catheter-related complications (visceral or vascular injury, wound breakdown, wound infection, intra-abdominal infection) and local anaesthetic systemic toxicity.

Sub-peritoneal catheter: a wound catheter placed beneath the parietal peritoneum.

Pre-peritoneal catheter: a wound catheter placed between the subcutaneous layer and parietal peritoneum.

Subcutaneous catheter: a wound catheter placed between the skin and subcutaneous layer.

6. Demarcation of study field

Not applicable as this will be a systematic review of published literature.

7. Ethical considerations

This study is a systematic review of published literature. There will be no contact with identifiable individuals and this will be a review of anonymized information in the public domain. This proposal will be sent as a no risk application to the University of Witwatersrand (WITS) Human Research Ethics Committee (Medical) and the Graduate Studies committee at WITS. Alternatively, an application for an ethics waiver will be sought from these committees.

Approval to conduct this systematic review has been obtained from Professor Palesa Motshabi Chakane, the Academic Head of the WITS Department of Anaesthesiology (see Appendix A).

8. Research Methodology

8.1 Research design

The design of this project will be a quantitative systematic review. This review will be performed in line with the reporting guidelines set out by Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) 2020 and the Joanna Brigg's Institute (JBI) Manual for Evidence Synthesis.

Depending on the quality of data collected, a quantitative meta-analysis may be undertaken.

8.2 Study population

The study population will include all patients reported on from randomised and non-standard randomised controlled trials (RCT) that meet the following criteria (identified across all searched databases):

1) Study population: all patients that have undergone an abdominal hysterectomy either through Pfannenstiel or lower midline incision as an emergency or elective procedure.

2) Study type: all randomised placebo or sham-controlled trials, including non-standard designs (such as cluster or crossover randomised controlled trials) and quasi-randomised trials.

3) Study intervention: any local anaesthetic at any dose that is continuously or intermittently administered for at least 24 hours via a multi-lumen catheter embedded within or adjacent to the surgical incision by the surgeon. The comparator arm must be continuous or intermittent wound administration of a placebo or a sham wound infusion.

8.3 Study sample

Sample size

All eligible articles that meet the inclusion and exclusion criteria will be included in the systematic review. Approximately 150 articles are expected to be returned from the combined electronic search of the relevant databases. These will be screened according to the relevant inclusion and exclusion criteria and be critically appraised before inclusion in the final systematic review.

Search strategy and study selection

The PubMed, Web of Science, Medline Complete, SCOPUS, PROQUEST, Cochrane and OVID databases will be searched until the end June 2022 using a structured search strategy (see Appendix C). The search strategy will be developed according to the PICO (Population Intervention Comparator/Control Outcome) framework. This strategy will be developed in consultation with a librarian at the WITS Health Sciences library.

Two review authors will independently determine eligibility of records from the database searched. The review authors will screen the titles and abstracts of all identified articles, and eliminate articles that are ineligible. Thereafter all duplicates will be removed. The review authors will then assess the full-text journal publications of the remaining citations for eligibility, according to the inclusion and exclusion criteria. In the event of disagreement, a third review author will independently adjudicate to reach a consensus. This entire selection process will be displayed in the form of a PRISMA flow diagram (see Appendix D).

A manual search of reference lists of all applicable studies will also be done to identify any other potential studies that may be included in this review.

Lastly, all identified articles to be included in the final systematic review will be subjected to critical appraisal. This process aims to assess the methodological quality of this study and aims to determine the extent to which the study has addressed the risk of bias in its design , conduct and analysis.

Inclusion criteria:

- Population:
    - Patients over the age of 18 undergoing total abdominal hysterectomy
    - Pfannenstiel incision or lower abdominal midline incision employed
    - Elective or emergency surgery
- Intervention:
    - Any local anaesthetic at any dose that is continuously infused or delivered through intermittent boluses, through a multi-lumen wound catheter embedded within or adjacent to the wound
    - Catheter can be subcutaneous, pre-peritoneal or sub-peritoneal
- Comparator/Control
    - Infusion of a placebo such as normal saline or a sham
- Outcome
    - Either postoperative pain score and/or postoperative opioid consumption
    - All secondary objective outcomes need not to be reported on as a criteria for inclusion
- Study type:
    - All randomized controlled trials including non-standard designs

Exclusion criteria

- Population:
    - Patients undergoing other types of hysterectomies (laparoscopic, vaginal or robotic-assisted hysterectomy)
- Intervention
    - Infusion through the wound catheter of agents other than local anaesthetics
- Comparator/Control
    - Studies where the comparator arm involved epidurals or peripheral nerve blocks
    - Studies with no placebo or sham as a comparison
- Outcome:
    - Studies that did not assess postoperative pain scores or postoperative opioid consumption
- Study type:
    - Observational studies such as cohort, case control, cross-sectional and case report/series studies

Critical appraisal tool

The JBI RCT critical appraisal tool (Appendix E) will be used to determine risk of bias, to ensure the validity of data presented by this systematic review. Two independent reviewers will individually critically appraise the articles according to the below 13 questions. Disputes will again be adjudicated by a third reviewer. A predetermined number of criteria will need to be met for studies to be included in the final analysis of this systematic review.

JBI RCT Appraisal Tool:

1) Was true randomization used for assignment of participants to treatment or control groups?
2) Was allocation to the treatment group concealed?
3) Were treatment groups similar at baseline?
4) Were participants blinded to treatment assignment?
5) Were those delivering treatment blind to treatment assignment?
6) Were outcome assessors blind to treatment assignments?
7) Were treatment groups treated identically other than the intervention of interest?
8) Was follow up complete? If not, were differences between groups in terms of their follow up adequately described or analysed?
9) Were participants analysed in the groups to which they were randomized?
10) Were outcomes measured in the same way for treatment groups?
11) Were outcomes measured in a reliable way?
12) Was appropriate statistical analysis used?
13) Was the trial design appropriate, and any deviation from the standard RCT design accounted for in the conduct and analysis of the trial?

8.4 Data collection

The review authors will independently review the entire full text of each of study that will be included in the final systematic review. The relevant information will be extracted and captured in both the JBI software package and a Microsoft Excel spreadsheet.
The following information from each applicable study will be collected:

1) Authors
2) Year of study

3) Year of publication
4) Country of origin of the study
5) Location of study and number of centres
6) Sample size (including sample allocated and analysed in each group)
7) Study inclusion and exclusion criteria
8) Indication and urgency of hysterectomy
9) Type and size of incisional wound
10) Location and type of wound catheter
11) Type and strength of local anaesthetic in the intervention group
12) Rate and duration of wound infusion, or intermittent bolus regimen
13) Details of placebo or sham used in the control group
14) Perioperative analgesic co-interventions and adjuncts, including rescue analgesia
15) Outcomes measured in order to assess primary and secondary objectives of this systematic review
    a. Postoperative pain at rest and on movement on postoperative day 1 (24 hours)
    b. Postoperative opioid consumption on postoperative day 1 (24 hours)
    c. Postoperative pain at rest and on movement after postoperative day 1
    d. Postoperative opioid consumption after postoperative day 1
    e. Postoperative opioid related adverse events
    f. Length of postoperative hospital stay
    g. Serious postoperative adverse events
16) Risk of bias (using the JBI critical appraisal tool)
17) Funding sources

The process of data extraction will follow the steps set out by the PRISMA 2020 guidelines (Appendix B).

In the event of missing or incomplete data, the trial authors will be contacted about any missing, unclear or unusable data. We will estimate the mean for continuous outcomes using the reported median and derive the standard deviation from the reported confidence interval, interquartile range or p-value. We will derive the number of events for dichotomous outcomes from the reported percentage of events.

The information gathered will then be used to create the quantitative synthesis component of this systematic review.

8.5 Data analysis

Descriptive statistics will be used to present the outcomes measured for this systematic review.

In the case of continuous data (pain scores, opioid consumption and length of hospital stay), mean differences or standardised mean differences will be used to present this data. For dichotomous data (opioid related adverse events and serious postoperative adverse events), the risk ratio or odds ratio will be used.

For both continuous and dichotomous data, a 95% confidence interval and p-value will be presented. A p-value of < 0.05 will be considered statistically significant.
The presence of statistical heterogeneity of outcomes across included trials will be assessed by using the I^2 test, where an $I^2 > 50\%$ indicates heterogeneity. Trials with significant heterogeneity will be reported as standardised mean differences and those without as mean differences.

If a meta-analysis is performed, overall effects in studies with significant heterogeneity will be reported using the random effects model and those without significant heterogeneity will utilise the fixed effects model.

The data analysis for both the systematic review and meta-analysis will be done with the assistance of a biostatistician using the JBI software package. Advice will be sought from the biostatistician in the case of missing or incomplete data in order to derive the above mentioned measures of effect.

9. Validity and reliability of the study

The validity of this study will be ensured by having two independent review authors searching for and identifying relevant studies to be included. The search process will be displayed as per the PRISMA 2020 flow diagram, to display the exact process. The JBI critical appraisal tool will also be independently applied by the two review authors as a final step before study inclusion to ensure methodological quality and to limit the risk of bias. A standardised data collection form will be used to capture all data, to improve reliability.

The search strategy for each database will be clearly outlined, to ensure that it is replicable and thorough. Seven databases will be searched to identify as many relevant articles as possible. Data extraction will also be done independently by two review authors to further ensure validity and reliability.
However, a few potential sources of bias remain, which include:

- Small study bias: small studies tend to be imprecise and overestimate the effect size. A few studies identified in the primary literature search have less than 50 participants which may lead to a bias in reported results.
- Attrition bias: occurs as a result of patients dropping out of a study or not being followed up diligently. The primary literature search has not identified high numbers of attrition. If this becomes a concern, intention to treat analysis will be performed.
- Industry bias: Industry sponsored trials tend to be more favourable to the sponsors' products, compared with non-industry-sponsored trials. This will be noted and will influence the grade of evidence in the final systematic review.
- Publication bias: unpublished or grey literature can be difficult to find and access. An attempt will be made to search databases that include clinical trials as well to search clinical trial registries.
- The EMBASE database will not be searched due to lack of access. However, it is likely that SCOPUS may pick up most articles listed on EMBASE as these database are both managed by Elsevier publications.

10. Potential limitations of the study

1. This study will only assess the effectiveness of local anaesthetic wound infusion following an abdominal hysterectomy only. The results are not generalisable to other types of hysterectomies such as vaginal and laparoscopic approaches.
2. This systematic review will assess the effectiveness of local anaesthetic wound infusion via wound catheters, which may be placed in different locations (subcutaneous, pre-peritoneal or sub-peritoneal) by a single outcome measure. This may affect the significance of the results. Possible subgroup analysis may be done to rectify this.
3. Local anaesthetic wound infusions will not be compared to epidural infusions (which may be considered the gold standard of regional analgesia) post abdominal hysterectomy according to current literature.

4. Incomplete or unusable data from included studies may lead to difficulty with the final statistical analysis, which may skew the true measured effect that is presented by this systematic review.

11. Project outline

11.1 Time frame

Year	2022											
Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature search												
Proposal												
Postgraduate approval												
Ethics approval												
Data collection												
Data analysis												
Draft review												
Submission												
Publication	Jan 2023											

11.2 Financial plan

Description	Price per item	Amount of items	Total
Printing proposal	R 25	5	R 125
Printing ethics form	R 2	3	R 6
Printing postgraduate form	R 2	5	R 10
Printing research report	R 100	4	R 400
Binding final research report	R 20	4	R 80
Paying for full text of studies which we don't have access to through the university	R 600	3	R 1800

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Appendices:

Appendix A – Letter of permission from Head of Department of Anaesthesiology, WITS

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
FACULTY OF HEALTH SCIENCES
WITS SCHOOL OF CLINICAL MEDICINE
DEPARTMENT OF ANAESTHESIOLOGY
Tel.(011)488 4344

11 March 2022

Postgrad Office

School of Clinical Medicine

Faculty of Health Sciences

University of the Witwatersrand

To Whom It May Concern

Permission To Conduct Research: Dr Hasmita Kooverjee

This is to confirm that I have read and given permission for **Dr Hasmita Kooverjee** to conduct research at in the Department of Anaesthesiology towards his/her Mmed project titled "***Local anaesthetic wound infusion for postoperative pain management following an abdominal hysterectomy: A systematic review"***

Thank you.

Assoc. Prof. P Motshabi Chakane

Ass Prof P. Motshabi Chakane
HOD Wits Anaesthesia
HOU Cardiac Anaesthesia
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WITS UNIVERSITY
WITS SCHOOL OF CLINICAL MEDICINE
FACULTY OF HEALTH SCIENCES

Appendix B – PRISMA 2020 reporting guidelines (58)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix C – Example of a search strategy for Medline Complete

1. MH "Hysterectomy") AND (MH "Anesthetics, Local")

2. hysterectomy AND local anesthetics

3. ((hysterectomy AND local anesthetics) AND (S1 AND S2)) AND (S1 AND S2)

4. hysterectomy AND local anaesthetic AND postoperative pain

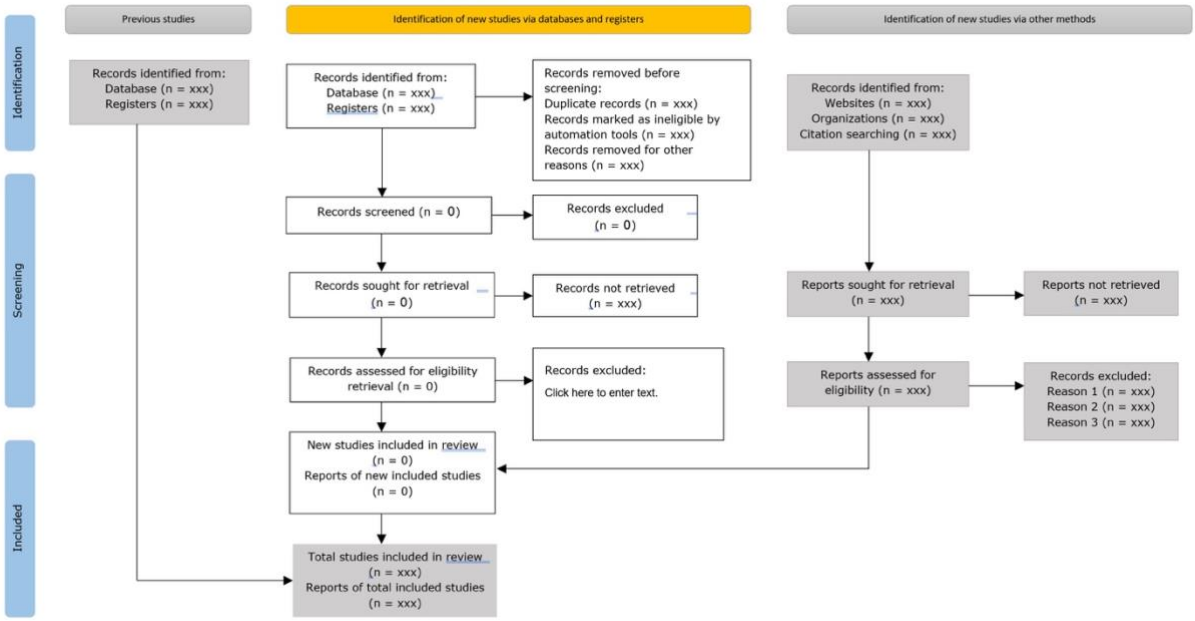
5. (S3 AND S4)

6. hysterectomy AND local anaesthetic infusion OR local anaesthetic infiltration OR wound catheter infusion OR local anaesthetic OR wound infiltration OR wound infusion OR continuous local anaesthetic wound infusion OR elastomeric balloon pump

7. (hysterectomy AND local anaesthetic infusion OR local anaesthetic infiltration OR wound catheter infusion OR local anaesthetic OR wound infiltration OR wound infusion OR continuous local anaesthetic wound infusion OR elastomeric ballon pump) AND (S5 AND S6)

8. hysterectomy AND continuous local anaesthetic infusion

Appendix D – PRISMA 2020 flow diagram (58)



Appendix E – JBI critical appraisal tool

Question	Yes	No	Unclear	Not applicable
1) Was true randomization used for assignment of participants to treatment or control groups?				
2) Was allocation to the treatment group concealed?				
3) Were treatment groups similar at baseline?				
4) Were participants blinded to treatment assignment?				
5) Were those delivering treatment blind to treatment assignment?				
6) Were outcome assessors blind to treatment assignments?				
7) Were treatment groups treated identically other than the intervention of interest?				
8) Was follow up complete and if not, were differences between groups in terms of their follow up adequately described or analysed?				
9) Were participants analysed in the groups to which they were randomized?				
10) Were outcomes measured in the same way for treatment groups?				
11) Were outcomes measured in a reliable way?				
12) Was appropriate statistical analysis used?				
13) Was the trial design appropriate, and any deviation from the standard RCT design accounted for in the conduct and analysis of the trial?				

Appendix 2. Post graduate approval for protocol amendments

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

29 June 2022
Person No: 539105
PAG

Dr H Kooverjee
P O Box 16
Kiasha Park
1829
South Africa

Dear Dr Hasmita Kooverjee

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Local anaesthetic wound infusion for postoperative pain management following an abdominal hysterectomy: A systematic review* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 3. Human research ethics committee clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Innovation)

20/06/2022

Ref: W-CBP-220620-01

TO WHOM IT MAY CONCERN

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)

Investigator: Dr H Kooverjee, et al
Student No. (if appropriate): 539105
Staff No. (if appropriate): A0043344

Supervisor: Dr J Moutlana

School: Clinical Medicine
Department: Anaesthesia
Medical School
University

Project title: *Local anaesthetic wound infusion for post-operative pain management following an abdominal hysterectomy: a systematic review*

Reason: Review of information in the public domain
No human participants will be involved in the study

Dr CB Penny
Chairperson: Human Research Ethics Committee (Medical)

Research Office Secretariat:
Third Floor, Phillip Tobias Building, corner of St Andrews and York Roads, Parktown, Johannesburg 2193
Postal address: Private Bag 3, Wits 2050
Tel Nos: +27 (0)11 717 1234/1252/2656/2700
Office E-mail: HREC-Medical.ResearchOffice@wits.ac.za
Website:
https://www.wits.ac.za/research/researcher-support/research-ethics/ethics-committees/

Appendix 4. Change of title approval letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

07 February 2024
Person No: 539105
TAA

Dr H Kooverjee
P O Box 16
Kiasha Park
1829
South Africa

Dear Dr Hasmita Kooverjee

Master of Medicine in Anaesthesia: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Medicine in Anaesthesia** has been approved:

From:	**Local anaesthetic wound infusion for postoperative pain management following an abdominal hysterectomy: A systematic review**
To:	**Local anaesthetic wound infusion for postoperative pain management following an abdominal hysterectomy: A systematic review and meta-analysis**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 5. Turn it in/ plagiarism report

turn it in draft 3.docx

ORIGINALITY REPORT

12%	8%	7%	9%
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