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Meta-analysis

Effectiveness of Bupivacaine as Pre-emptive Pudendal Block among Patients Undergoing Vaginal Surgeries: A Systematic Review

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Abstract

Background: Pre-emptive analgesia using pudendal nerve block (PNB) with bupivacaine is commonly used in clinical practice during perineal, pelvic floor or vaginal surgeries. However, its effectiveness is unclear. We conducted this review to synthesize short- and intermediate-term outcomes of pre-emptive analgesia using pudendal nerve block with bupivacaine.

Methods: We searched the CENTRAL, PubMed, ClinicalTrials.gov, Google Scholar, and Open Grey from inception until April 2020. Randomized controlled trials (RCTs) of women who underwent perineal, pelvic floor or vaginal surgeries and received pre-emptive analgesia using a pudendal nerve block were included. Two authors independently screened, selected and performed data extraction as well as quality assessment on eligible trials. Disagreements were resolved via consensus. Data were narratively synthesized; when possible, data were pooled in RevMan 5 using the random-effects model.

Results: Four RCTs with a total of 349 participants were eligible for inclusion. We found evidence of improvement in post-operative pain scores; requirements for opioids, standardized mean difference (SMD): -0.89 (95% CI: -1.19, -0.59) and non-steroidal anti-inflammatories SMD -1.04 (95% CI: -1.64, -0.43) in favor of the PNB versus control group. The risk ratio for adverse effects of postoperative nausea and vomiting, 0.42 (95% CI: 0.18, 0.99) favored PNB. There was no significant difference between groups for the length of hospital stay, mean difference -0.82 (95% CI: -5.34, 3.69) and return to regular activity.

Conclusion: We found limited evidence that pre-emptive pudendal block using bupivacaine improves postoperative pain and recovery in perineal, pelvic floor or vaginal surgeries. However, due to the heterogeneous nature of evidence, well-designed RCTs are required.

Keywords: Pre-emptive Analgesia, Bupivacaine, Pudendal Nerve Block, Vaginal Surgery, Pelvic Organ Prolapse, Meta-Analysis

Introduction

Clinical goals of early ambulation, discharge, and rehabilitation in gynecological surgery were introduced approximately two decades ago.[1] In the US, approximately 200,000 women undergo vaginal surgery each year due topelvic organ prolapse (POP). The prevalence of surgical interventions for POP is projected to rise from 8% to 45% over the next 30 years.[2,3] Pain management is a vital element of patient care after vaginal reconstruction.[3,4] Different multimodal pain management techniques are used to achieve better outcomes.[3] Pudendal nerve block (PNB) is a low-risk, low-cost, anesthetic technique, used to effectively reduce perineal and vaginal discomfort during repair of obstetric lacerations.[5] It is administered at the sacrospinous ligament and provides highly effective and safe anesthesia to the vulva, lower vagina, and perineum.[6,7]

Pre-emptive analgesia is also widely used in many surgical procedures such as laparoscopy, hemorrhoid-dectomy, penile prosthetic surgery and circumcision.[8-11] Various pre-emptive treatment modalities and their combinations have been evaluated.[2,4,12-14] The effects

of pre-emptive analgesia may vary according to the type of surgery, particularly, vaginal surgery, and pain management to recommended levels have not yet been observed.[5,7] Various gynecological procedures are currently performed using regional nerve block or with local infiltration, such as cervical cerclage, dilatation and evacuation, and perineal procedures.[6,7,15] Different local anesthetics are used, such as lidocaine, bupivacaine, and mepivacaine.[15] Onset of action typically within 5 to 10 minutes and duration of action between 1 to 2 hours. Bupivacaine has a time of onset of action of 5 minutes, a duration of 4 hours with 2 mg/kg dose and up to 7 hours with epinephrine at 3mg/kg dose.[15,16]

Bupivacaine is a highly soluble lipid commonly used as an agent for peripheral nerve blocks.[17,18] However, the use of Bupivacaine in PNB has shown controversial results.[3,19] Positive outcomes for the effect of bupivacaine on different nerve blocks in the abdominal and perineal region have been reported.[5-10] However, these results do not show effectiveness when compared against minimum clinical differences in postoperative pain.[2,4,20,21] Pain originates from multiple points during surgery and outcomes withpre-emptive analgesia vary with different surgical approaches.[2,3] For pelvic reconstructive surgeries, evidence of efficacy is uncertain and important considering the rising number of surgeries performed.[2,3] Therefore, evaluating the efficacy and safety of postoperative pain management techniques that enhance patient recovery would have potential implications within clinical practice.[2,3] We aimedto synthesize evidence from randomized controlled trials evaluating pre-emptive analgesia administered as aPNB for vaginal surgery.

Objectives

To evaluate the effectiveness of pudendal nerve block using bupivacaine among women undergoing perineal or vaginal repair surgery. The primary and secondary outcomes were postoperative VAS scores at 24 hours and requirement for additional analgesics, respectively. Other secondary outcomes considered include adverse effects of post-operative pain, recovery time, patient satisfaction and surgeon satisfaction.

Materials and Methods

Protocol Registration and Search Strategy

This systematic review was conducted using recommendations by PRISMA guidelines.[22] Details of the study protocol was registered on PROSPERO website, registration number:CRD42019118890.

Eligibility Criteria

The eligibility criteria were selected using the participant, intervention, comparison and outcomes (PICO) criteria. We included all randomized controlled trials that evaluated the effect of pre-emptive nerve block among women diagnosed with pelvic organ prolapse (POP) who underwent perineal or vaginal repair surgery. The intervention of interest was a pudendal nerve block achieved using bupivacaine. The comparators included a control group consisting of either general anesthesia alone, spinal anesthesia with or without injecting normal saline. We evaluated clinical acute and intermediate outcomes of postoperative pain, consumption of additional analgesics, adverse effects, recovery time, patient satisfaction and surgeon satisfaction. However, we did not exclude studies using this criterion while screening at title or abstract.

We excluded studies describing or comparing surgical procedures that involve additional laparoscopic procedures or where the procedure involved high nerve involvement like hysterectomy or laparoscopic-assisted vaginal hysterectomies. Studies or clinical trials that enrolled male participants used surgical interventions for obstetrics or anal disorders, or measured gluteal pain instead of perineal pain, delivered nerve block after surgery; used different anesthetic agents like ropivacaine and lidocaine; used different routes of local analgesia; evaluated an additional operative procedure like laparoscopy or measured different outcomes like gluteal pain were excluded. Reviews, letters, observational studies such as case-controls, cohort studies, case reports and case series were also excluded.

Information Sources and Search Strategy

We systematically searched the following electronic databases of CENTRAL, PubMed, ClinicalTrials.gov, Google Scholar and Open Grey from database onset until April 2020. Combined MeSH terms, keywords, and National Institute of Health search filters to develop a sensitive search strategy using the study population and intervention criteria. Keywords of the population (gynecologic surgical procedures) and intervention (Bupivacaine) were also used to search databases of google scholar and the grey literature (Open Grey). Condition-specific search terms of

gynecologic surgical procedures, pelvic organ prolapse, pelvic floor disorders, anterior and posterior vaginal repair, colpopexy, colpoperineorrhaphy, perineum or perineal surgery and pudendal nerve block or bupivacaine were then combined. We did not restrict records by language, date, publication status or outcomes during the search process. All articles identified were retrieved and uploaded into a reference manager.

Study Selection

All articles were transferred into a systematic review web application - Rayyan for independent screening.[23] The titles and abstracts of studies were independently screened by two reviewers (MR and JT) to exclude irrelevant studies. Differences of opinion were to be resolved by discussion when a consensus was not achieved, a third review author (AA) was consulted. Full texts of potentially eligible articles were then independently reviewed using the study inclusion criteria to identify eligible. At title and abstract screening, if it was unclear whether a study evaluated postoperative pain after perineal, vaginal or pelvic surgery, postoperative pain scores or primary outcomes of interest, then the study was retained for full-text review. At the full-text review, randomized controlled trials were screened using the study eligibility criteria. Articles that evaluated bupivacaine as pre-emptive analgesia for women undergoing perineal, vaginal or pelvic floor surgery were retained for qualitative synthesis and when possible, depending on the availability of data were meta-analyzed.

Data Extraction

Two reviewers (JT and MR) independently extracted data from eligible studies using a standardized extraction form that was designed using guidance from the Cochrane Handbook for Systematic Reviews of Interventions and piloted before use.[24] We extracted the following characteristics of records: authors and year of publication, study type or design, location, setting, inclusion criteria of the population such as age; metabolic index or its derivatives and stage of prolapse; sample size; study attrition; duration of follow-up; inception time (time between presentation for surgery and recruitment to trial); type of intervention (dosage, type of nerve block, frequency of administration and approach or method of delivery); outcome measures such as adverse effects and estimates [means(standard deviations) or median (ranges)] if provided; follow-up time points (short, medium and long-term) and methods used to analyze results. We contacted authors of eligible studies when insufficient data were reported. For studies with duplicate, companion or overlapping records, recent publications were used when findings were similar. When records were different, a comprehensive primary source was selected, while complimentary data was extracted from duplicate records.

Data Synthesis

We narratively synthesized the results of included studies when a) data was insufficient to assess pre-specified outcome comparisons, b) outcomes or estimates were incompletely reported, c) significant evidence of skew or bias in evidence was identified, and d) significant clinical or statistical heterogeneity was identified. Due to anticipated heterogeneity, a meta-analysis was performed using a random-effects model with RevMan 5.3 Software (Cochrane IMS). Comparisons of pudendal nerve block versus control as intervention components were considered and meta-analyzed. When two or more studies reported an outcome, we combined mean differences (MD) and standard deviations (SD) to provide summary estimates for continuous measures using an inverse variance method to estimate the difference.

Standardized mean differences (SMD) were used when different assessment tools are used to measure and report outcomes. Multiple pain assessment time points were defined as short-term for outcomes measured up to and including four weeks after surgery and intermediate-term when outcomes when measured at greater than 4 weeks after surgery. Subgroup analysis was considered for indications of perineal surgery if there were sufficient trials. For dichotomous outcomes, we used the Mantel-Haenszel method to estimate relevant effect estimates (such a relative risk, risk ratio and odds ratio) and corresponding confidence intervals were calculated. Where ordinal data were used to measure outcomes, for example, satisfaction rates, categories were collapsed, and the data dichotomized.

Assessment of Heterogeneity

We assessed studies included in this review for

evidence of clinical heterogeneity, in either the characteristics of the participants, the interventions or the outcomes. When it was evidence that pooling the studies was appropriate, statistical heterogeneity between the results of different studies was examined by formally checking the results of the Chi2 test, using a *p* value of less than 0.10 as evidence of significant heterogeneity.[24] This approach was chosen due to the low power of the chi-square test when clinical and statistical heterogeneity is anticipated.

The I^2 statistic was also checked to determine the percentage of total variation across studies due to heterogeneity rather than chance.[24] Heterogeneity was explored using the Chi-squared test and I^2 statistic, with a probability value of <0.10 indicating significant heterogeneity. Findings were interpreted using the following: I^2 of 0% to 30%, unimportant heterogeneity; 30% to 60%, moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, high heterogeneity. In cases with extreme statistical heterogeneity unexplained by differences between studies, the estimates were not pooled in the meta-analyses.

Assessment of Study Quality

Two review authors (MR and JT) independently assessed the risk of bias using the Cochrane risk of bias tool.[25] We considered the following domains: random sequence generation (whether the allocation sequence was adequately generated using a random number generator) and whether the allocation was adequately concealed, for example, using opaque sealed envelopes. Blinding of participants, personnel and outcome assessors during the conduct of the study was assessed; knowledge of the intervention is likely to influence the outcomes and whether an incomplete outcome or missing data were adequately addressed or recorded.[25]

Selective outcome reporting checks whether the study is free of selective outcome reporting when compared against a published study protocol or pre-specified analysis. We also checked whether the study was free of other sources of bias that could bias findings, for example, baseline imbalance between groups. Each domain was scored as either low risk (when the criteria were met); unclear risk (uncertainty perhaps due to poor reporting standards) or high risk (when the criteria were not met).The effects of publication bias would be considered only based on available data (more than 10 studies)[26] Sensitivity analysis was considered to explore the effects of risk of bias on the results.

Assessment of Quality of Evidence

Two review authors (MR and JT) independently assessed risk of bias using the Cochrane risk of bias tool developed by GRADE (Grading of Recommendations, Assessment, Development and Evaluations) collaboration.[27] Findings were summarized in a summary of findings table (SoF) using GRADE. We considered the influence of risk of bias, inconsistency, generalizability, imprecision and publication bias on effect estimates. The GRADE assessment score was downgraded accordingly when any of these factors when judged as present for each evidence found. Each factor was downgraded from high to very low using the following guidelines: greater than 25% of the participants were from studies with a high risk of bias; significant heterogeneity was identified or if substantial differences in magnitude and direction of effects between studies was present. For imprecision, this was poorly rated when >50% of the participants are outside the target group; and single studies with <400 participants for continuous outcomes or <300 participants for dichotomous outcomes.[28]

Results

We identified 968 records that were potentially eligible for inclusion. After removing 63 duplicate studies, 905 records were screened for eligibility. 845 studies were excluded at the title and abstract screening; 17 studies were included for full-text review. At the full-text screening, thirteen studies were excluded.[15,29-38] Six studies included patients undergoing abdominal hysterectomy, laparoscopy with perineal/vaginal procedures or obstetric surgery;[15,31,32,35-37] 3 studies were trial registrations of full texts that were already included in the review;[29,30,33] 3 studies used different interventions, e.g. sacrocolpopexy;[34,38,39] and one study assessed a different outcome-gluteal pain instead of perineal pain.[16] One study[15] reported a subgroup analysis of a relevant intervention arm. We contacted the corresponding author[15] for the unpublished results, but the authors did not respond (Figure 1).

Included Studies

We identified four randomized controlled trials[2,4,20,21] that met our eligibility criteria and were included in the

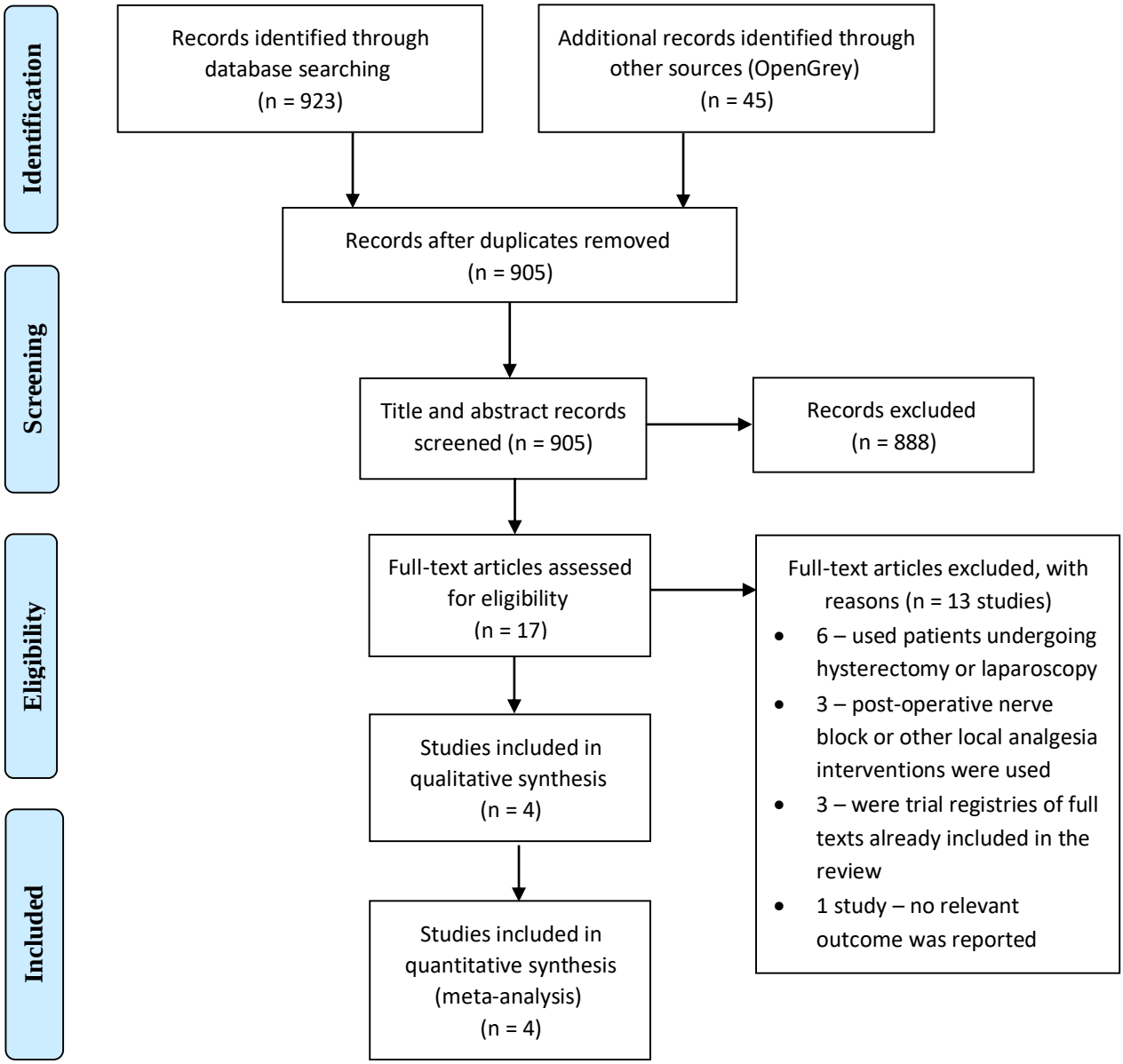

Figure 1. Showing the Study Selection Process for a Systematic Review of Pudendal Nerve Block Using Bupivacaine.

review (Table 1). All studies used randomized parallel studies that provided a total of 349 women, but not all data from participants were included in the analysis of every outcome. The sample size ranged from 57 to 130, with power calculations reported for all of the included studies.[2,4,20,21] While the mean age ranged from 33.1 ± 6.2 to 61.2 ± 14.0 years. One study[2] reported incomplete data that was unclear and not available even after contacting the primary author. All trials were single-center studies, published in English, conducted in the USA,[4] Lebanon,[21] Iran,[2] and Kuwait.[20] No study provided details on sources of funding or trial registration. There was significant heterogeneity between studies included in this review and insufficient number of trials to assess publication bias.

Risk of Bias Assessment of Included Studies

All studies[2,4,20,21] reported randomly allocating participants into groups using computer-generated numbers. One study[2] did not report performing adequate allocation concealment. All studies reported adequate blinding for study participants. Three studies[4,20,21] reported adequately blinding surgeons, while only three studies[4,21] used blinded outcome assessors.

Table 1. Characteristics of the Included Studies

Study	Participants	Diagnosis for procedure and surgical approach	Specifics of the intervention(s)	Outcomes	Results
Abramov 2005[4]	IG: GA+PNB n = 51 Sample loss = 2 Mean age: 61.2 (SD 14) yrs Median Parity: 3(0-7) BMI (kg/m^2): 28.9 (SD 14) PPOP Stage: II: 33 (66) III: 12 (24) IV: 6 (12)	Inclusion criteria: -Women undergoing transvaginal pelvic reconstructive surgery under general anesthesia. -ASA physical status I-II Exclusion criteria: -Intolerance to local anesthetic agents or narcotics -Coagulation disorders -ASA physical status of more than II -History of a major psychiatric disorder chronic pain syndromes, substance abuse -Current opioid use or planned procedure for urinary incontinence	Intervention, PNB: Pre-emptive pudendal nerve blockade with 10 mL of 0.25% bupivacaine bilaterally. Procedure: After general anesthetic induction, each patient received a 10-mL pudendal nerve block injection on each side as per pudendal block protocol. After 2 hrs, if surgery was still in progress, an additional 5-mL pudendal nerve block was administered on each side. Co-interventions: Analgesic requirements either intravenous hydromorphone or ketorolac consumption. Thirty-two participants (63%) from the bupivacaine group and 30 participants (59%) from the saline group received a second pudendal block injection due to prolongation of their surgery beyond 2 hrs.	1- VAS 2- Additional post-operative analgesic requirements at 3, 7, 18, and 24 hrs after surgery 3- Medical and surgical complications 4- Length of hospital stay	- The mean change in the VAS (10cm) pain scores showed no significant improvement in the intervention group compared to the control group - No significant difference between the 2 groups was found for consumption of intravenous hydromorphone (1 mg), additional boluses of hydromorphone (15 mg), ketorolac (1 mg) or analgesics (mg/hr) at all assessment times. -No significant differences in hospital stay (39.6 hrs versus 37.3 hrs) or complication rates (nausea/vomiting, itching or respiratory depression) were found between groups.
	CG: GA+ normal saline n = 51 Sample loss = 2 Mean age: 58.6 (SD 13) yrs Median Parity: 3(0-10) BMI (kg/m^2): 29.2 (SD 16) PPOP Stage: II: 34 (68) III: 11 (22) IV: 6 (12)		Control: Pre-emptive pudendal nerve blockade with 10 mL of normal saline (0.9%) bilaterally. Co-interventions:Same as in IG		

Ismail 2012[17]	IG: GA+PNB n = 65 Sample loss = 0 Mean age: 34.5 (SD 5.9) yrs. Mean Parity: 4.6 (SD 2.1) BMI (kg/m^2): <25: 35 (53.85) 25-30: 24 (36.92) >30: 6 (9.23)	Inclusion criteria: -Women scheduled for posterior colpoperineorrhaphy -ASA physical status I–II -Age between 25 and 45 yrs Exclusion criteria: -Intolerance to local anesthetic agents or narcotics -Coagulation disorders -ASA physical status of more than II -History of a major psychiatric disorder, chronic pain syndrome or substance abuse -Current opioid use. Procedure: General anesthesia combined with pre-emptive analgesia by bilateral nerve stimulator-guided pudendal nerve block with 10 mL of 0.25% bupivacaine.	Intervention, PNB: After general anesthesia, pre-emptive analgesia by bilateral nerve stimulator-guided pudendal nerve block (group II) with 10 mL of 0.25% bupivacaine to each side was performed using transperineal approach. Co-interventions: -Analgesics was provided after surgery (transvaginal approach) during hospital stay. Pethidine (1 mg/kg for 24 hr) for participants with VAS score of > 50mm and paracetamol IV infusion (mg/24 hr) for participants with VAS score of 30-50mm to max of 1g/6hrs. for participants with VAS score <30mm no supplemental analgesics was administered.	1- 24hrs VAS (0-100mm) 2-Post-op analgesic consumption 3-Adverse effects of pudendal nerve block 4-Medical and surgical complications 5-Length of hospital stay 6-Resumption of normal activities measured @ clinic day 4, 8 and 14 after discharge 7- Overall patient satisfaction score (1-4-point verbal scale ranging from very satisfied to very dissatisfied) with analgesia (24 hrs after operation)	-Average postoperative VAS pain scores (p <0.0001) -IM pethidine and IV paracetamol consumption (mg/24hr) were significantly lower in the PNB group compared to the control (p <0.0001) -PNB group showed a shorter recovery room stay (hr) compared to the control group (p < 0.0001) -No significant difference was observed for post-operative nausea (p=0.38), vomiting (p=0.40) and urinary retention (p=0.09) -PNB group showed higher discharge rates (days) (p<0.0001) and quicker return to normal activities (days) compared with the control group (p < 0.0001) -Overall patient satisfaction score with analgesia and pain reliefwas significantly higher in the PNB group compared to control group (p <0.0001).
	CG: GA only n = 65 Sample loss = 0 Mean age: 33.1 (SD 6.2) yrs. Mean parity: 4.3 (SD 2.0) BMI (kg/m^2): <25: 32 (49.23) 25-30: 26 (40.0) >30: 7 (10.77)		General anesthesia alone Co-interventions:Same as in IG		
Rouholamin 2015[3]	IG: Spinal anaesthesia + bupivacaine 0.25% n = 30 Sample loss = NR Mean age: 41.9 (SD 7.1) yrs	Inclusion criteria: -Women undergoing anterior posterior repair under spinal anaesthesia performed using the same technique and by the same Gynecologist. -ASA status I and II Exclusion criteria: -No history of allergy to local anesthetic agents and narcotics	Intervention, PNB: The spinal block was done with 3 cc bupivacaine 0.25% in10-15s. -Stimulator-guided pudendal nerve block.The solution was injected in the pudendal nerve passage way by nerve stimulator in both groups at the same period of anesthesia. Co-interventions: -Both groups received the same	1-VAS from 0-48hrs 2-SBP and DBP (mmHg) from 0-48hrs 3-Heart rate and Respiratory rate (bpm) from 0-48hrs 4- Total analgesic Pain relief medication bolus (0.08 mg/kg morphine)recorded at 2, 4, 6, 12, 24 and 48 hrs after surgery 5- Nausea and vomiting	-Significant differences in changes in pain intensity at rest with higher pain levels (hrs) in the control group compared with the PNB group (p=0.003) and while standing (p=0.021). No significant difference in change was found in sitting position (p=0.34) -Mean changewithin and between groups in systolic

		-No history of clotting problems -No history of major psychological disorders -No history of chronic pain syndrome	post-op. care of additional IV bullous of morphine 0.08 mg/kg until VAS was <3 and monitoring for up to 48hrs.	managed with metoclopramide (0.15 mg/kg). 6-Complication rate at 48-hrs post-operatively	(p=0.2) and diastolic blood pressure (p=0.15) were not different in the intervention and control arms.
	CG: spinal anaesthesia + 0.3 cc/kg normal saline n = 30 Sample loss = NR Mean age: 41.6 (SD 10) yrs	-Lack of long-term use of painkillers -No recent use of opioids -Lack of diabetes mellitus type 1 and 2 -Need to change the type of anaesthesia during surgery (due to prolongation of the operation or failure to block). Procedure: Both groups received the same pre-operative care and spinal anaesthesia.	Control: The block was done with0.3 cc/kg normal saline for the control group was injected in the pudendal nerve passage way using a nerve simulator at the same period of anaesthesia. Co-interventions: same as in IG	7-Sedation scores 0-48hrs post-operation	-Mean changes in HR (P=0.47) and RR (P=0.81) were not significantly different between groups. -Morphine consumption was only significantly higher in the control group at 4 and 12 hrs after surgery. -No difference was identified in the frequency of incidence of nausea and consumption of metoclopramide. -At 48hrs post-operatively, no difference in complication rates were identified between the PNB and control groups -No significant differences (p = 0.41) in between group mean sedation scores from 0-48hrs was identified
Khalil 2016[18]	IG: GA+PNB n = 28 Sample loss = 0 Mean age: 43.4 (SD 12.7) yrs Weight: 70.2 (13.2) kg Height: 158.4 (7.9) cm Stages of pelvic organ prolapse: I-11(39.3%) II-10(35.7%) III- 5(17.9%) IV- 2(7.1%)	Inclusion criteria: -Participant between 20 and 53 yrs -Scheduled to undergo AP colporrhaphy due to cystorectocele. Exclusion criteria: -Participants who are allergic to any of the local anesthetics. -Have distorted anatomy due to previous surgery such as episiotomy, -Have any concurrent surgery -Refused to participate in the study.	Intervention, PNB: Every 30 mL of the local anesthetic mixture contained 2% lidocaine 10 mL, 2% lidocaine 10 mL with adrenaline 5 µg/mL, 0.5% bupivacaine 9.5 mL, and clonidine 0.5 mg (75 µg). A 22G 10-cm nerve stimulator needle was used as per protocol. Co-interventions: Intravenous analgesicsof paracetamol or ketoprofen once/dayfor VAS 3-4; tramadol hydrochloride 50-100 mg every 4-	1- VAS at (6, 12, 24, 36, and 48 hrs). 2-Pain relief medication bolus (morphine) 4- MAP 5-Post operative nausea and vomiting PONV 6- Return to normal activity 7-Patient satisfaction 8-Surgeon satisfaction 9-Medical or surgical complications	-Significant difference in average postoperative pain scores over 48 hrs (P =0.015). -Total analgesic consumption (ketoprofen and tramadol) was lower in the PNB group during the first 48 hrs. -Significantly lower MAP in the PNB group compared with GA group during (87.6 vs 99.9, P =.002) and at the end of operation (91.1 vs 102.2, P < .0001). -PONV was minimal in the

		6 hrs, max. 400 mg/day for VAS scores 4-5; morphine (0.1-0.2 mg/kg) for VAS scores >5. Participants in stages I and II required propofol sedation and stages III and IV required propofol and sevoflurane.	PNB group compared with the GA group (3.6% vs 41.4%). -Return to normal daily activity was significantly (P = .015) shorter in the PNB group compared with GA group (3.6 vs 12.2 days). -Patient satisfaction was significantly (P = .006) greater in the PNB group. -Surgeons who performed the operation with the PNB group were significantly (P = .005) more satisfied than those from the GA group. -None of the participants had hematoma, infection, or persistent paraesthesia secondary to the nerve blocks
CG: GA alone n = 29 Sample loss = 0 Mean age: 40.8 (SD10.2) yrs Weight: 75.7 (12.9) kg Height: 158.5 (6.7) cm Stage of pelvic organ prolapse: I-12(41.4%) II-10(34.5%) III- 6(20.7%) IV- 1(3.4%)		General anesthesia alone. Co-intervention same as in IG.	

IG: Intervention group; GA: General anesthesia; PNB: Pudendal nerve block; yrs: Years; BMI: Basal metabolic index; kg/m^2: Kilogram per square metre; PPOP Stage: Preoperative pelvic organ prolapse; Ml: Milli-litres; %: Percentage; cm: Centimetres; VAS: Visual analog scale; F: Female; *p*: *p*-value; CG: Control group; hr: Hour; /: Per; Hz: Hertz; mA: Micro-ampoules; IV: Intravenous; IM: Intramuscular; mm: Millimetres; post-op-Post-operative; NR: Not reported; cc: Cubic centimeter; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; bpm: Beats per minute; MAP: Mean arterial blood pressure; mmHg: Millilitres per mercury; PONV: Post-operative nausea and vomiting.

Table 2. Risk of Bias Ratings for Randomised Studies Using Cochrane Risk of Bias

Abramov 2005 (4)	Ismail 2012 (17)	Rouholamin 2015(3)	Khalil 2016 (18)	Trial characteristics	Classification
					× High risk of bias
					? Some concerns
					✓ Low risk of bias
✓	✓	?	✓		Randomisationprocess
✓	✓	✓	✓		Deviation from intended interventions
✓	?	×	×		Measurement of the outcome
✓	✓	✓	✓		Missing outcome data
✓	✓	✓	✓		Selection of the reported result
Low	Some concerns	Some concerns	Low		Overall risk of bias

All studies[2,4,20,21] reported adequate methods for all other domains of risk of bias assessment. There was no evidence of other risks of bias due to imbalance or selective outcome reporting. However, the reporting standards were poor for two[2,20] out of the four[2,4,20,21] studies (Table 2).

GRADE Summary of Findings

All outcomes were judged to have a low or very low level of evidence (Table 3). This was mostly due to high risk of bias within individual studies, inconsistency in the direction of results and imprecision due to the inadequate number of participants used to evaluate outcomes. No study assessed outcomes of incomplete analgesia, systemic toxicity, hematoma formation, cost-effectiveness analysis and quality of life.

Primary Outcome

Postoperative VAS Scores at 24 Hour

Three studies[20,21] provided data (n=349) for postoperative pain but were not combined in a meta-analysis due to substantial heterogeneity. The results of the individual studies showed improvement in patient-reported pain among women receiving bupivacaine for PNB compared with women in the control group (Table 4). One study[20] showed standardized mean difference, SMD of -2.56 (95% CI: -3.03, -2.10) in favor of PNB and another study[21] showed SMD of -0.83 (95% CI:-1.37, -0.29). The results reported by one study[4] suggested that the data was skewed. The authors[4] reported insignificant differences in the postoperative pain outcomes between intervention and control groups, a median of 3 (range: 0-10). One study[2] described improvement in the PNB group compared to the control but did not provide data to support their findings, even after attempts to contact the corresponding author.

Secondary Outcomes

The Requirement for Additional Analgesics

Three studies[2,4,21] provided data used to assess the effect of PNB on the requirement for additional analgesics (Table 5a). We performed a subgroup analysis

Table 3. Summary of Findings Table – GRADE Levels of Evidence

Outcome	Participants	Design	RoB	Inconsistency	Indirectness	Imprecision	Publication Bias	Certainty
Post-op VAS scores	349	4 RCTs	Very serious	Very serious	Not serious	Serious	Not assessed	Very Low*
Total analgesic consumption	289	3 RCTs	Not serious	Very serious	Not serious	Serious	Not assessed	Low*
Postoperative nausea and vomiting	349	4 RCTs	Very serious	Not serious	Not serious	Serious	Not assessed	Low
Intravenous hydromorphone	102	1 RCT	Not serious	NA	Not serious	Serious	Not assessed	Low‡
Return to activity (days)	187	2 RCTs	Very serious	Not serious	Not serious	Serious	Not assessed	Low
Total length of hospital stay (hours)	232	2 RCTs	Very serious	Very serious	Not serious	Serious	Not assessed	Very Low
Surgeon satisfaction with procedure	57	1 RCT	Unclear	NA	Not serious	Serious	Not assessed	Very Low‡
Patient satisfaction with management	187	2 RCTs	Not serious	Not serious	Not serious	Serious	Not assessed	Low#
Other Adverse events(*requirement for additional intraoperative sedation)*	57	1 RCT	Not serious	NA	Not serious	Serious	Not assessed	Low‡
Incomplete analgesia	Not measured	-	-	-	-	-	Not assessed	No evidence
Hematoma formation	Not measured	-	-	-	-	-	Not assessed	No evidence
Cost-effectiveness	Not measured	-	-	-	-	-	Not assessed	No evidence
Quality of life	Not measured	-	-	-	-	-	Not assessed	No evidence

RoB: Risk of bias; *Complete data from one study unavailable; NA: Not applicable; Downgraded for being a single study‡; Downgraded for being reporting bias#.

Table 4. Primary Outcome of Included Studies – VAS

Outcome	Arm\Study	Abramov 2005[4]	Ismail 2012[17]	Rouholamin 2015[3#]	Khalil 2016[18]
Average postoperative VAS pain scores (mm/cm)	PNB	(VAS: 0-10 cm) Median (range) 1 hr: 4 (0-10) 3 hrs: 3 (0-10) 5 hrs: 3 (0-9) 7 hrs: 2 (0-9) 18 hrs: 3 (0-9) 24 hrs: 3 (0-10)	24 hrs post-operation (VAS: 0–100 mm) 23.5 (SD 7.4)*	1 hr 2 hrs 4 hrs 6 hrs 12 hrs 24 hrs 48 hrs	(VAS: 0–10 cm) Within first day: 2.1 (SD 1.0) Within the second day: 1.5 (SD 1.2)*
	Control	1 hr: 5 (0-10) 3 hrs: 4 (0-8) 5 hrs: 4 (0-8) 7 hrs: 3 (0-8) 18 hrs: 4 (0-9) 24 hrs: 3 (0-8)	51.1± (SD 13.2)	1 hr 2 hrs 4 hrs 6 hrs 12 hrs 24 hrs 48 hrs	Within first day: 2.9 (SD 0.9) Within the second day: 2.7 (SD 1.8)

#Results for this study is unavailable, authors were contacted for complete data with no reply; VAS: visual analog scale; mm: millimetre; cm: centimetre; PNB: Pudendal nerve block; hr: hour; SD: standard deviation; *p*: *p*-value; significant difference from pre-test; *$p<0.05$; **$p<0.001$.

Table 5a. Secondary Outcome Measures Reported as Continuous Outcomes

Study	Outcome	Time-point	PNB	Control
Abramov (2005)[4]	1 mg bolus of Intravenous hydromorphone consumed [Mean (SD)]	0-3 hrs	1.84 (1.15)	1.77 (1.13)
		4-7 hrs	1.19 (0.97)	1.20 (0.83)
		8-18 hrs	2.89 (2.59)	2.35 (2.77)
		Total hrs	5.92 (3.91)	5.32 (2.48)
	Total hydrocodone (500 mg /24hr) [Mean (SD)]	Every 4hrs	10.6 (9)	12.7 (11)
	Total ibuprofen (600 mg /24hr) [Mean (SD)]	Every 6 hrs	630 (779)	762 (716)
	Total hospital stay (hr) [Mean (SD)]	-	39.6 (14)	37.3 (13)
Ismail (2012)[17]	Total pethidine IM (mg/24 hr) [Mean (SD)]	24 hrs	239.4 (30.7)	278.3 (45.9)
	Total paracetamol IV infusion (mg/24 hr) [Mean (SD)]	24 hrs	2.0 (0.5)	2.6 (0.4)
	Overall patient satisfaction score with analgesia 24 hr after operation) [Mean (SD)]	24 hrs	3.4 (0.6)	2.8 (0.7)
	Total hospital stay (hr) [Mean (SD)]	-	25.86 (2.68)	28.38 (3.24)
	Resumption of normal activities (days) [Mean (SD)]	4-14 days	7.71 (1.1)	8.67 (0.9)
Khalil (2016)[18]	*Analgesic consumption [Mean (SD)]*			
	Ketoprofen	First 48 hrs	232.1 (190.6)	346.4 (129.1)
	Tramadol	First 48 hrs	35.5 (54.7)	96.6 (109.7)
	Return to normal activity (days)	-	3.6 (3.1)**	12.2 (2.9)

PNB: Pudendal nerve block; SD: Standard deviation; hr: hour; mg: milligram; VAS: visual analog scale; IM: Intramuscular; IV: intravenous; *$p<0.05$; **$p<0.01$; ***; $p<0.001$.

for additional analgesic requirements. Using data from 2 studies (n = 187), we found no difference between groups for the requirement for opioids SMD of -0.49 (95% CI: -1.25, 0.26) and low confidence in the certainty of evidence. Data pooled from 2 studies (n = 187), with a low level of evidence showed a significant difference SMD: -0.73 (95% CI: -1.45, -0.01) for NSAIDs (non-steroidal anti-inflammatory drugs) between the intervention and control groups. However, the results of a sensitivity analysis after excluding the study by Abramov[4] showed significant differences in additional consumption of analgesics in favor of the PNB arm compared to the control arm.

For opioids, we found SMD of -0.89 (95% CI: -1.19, -0.59) and for NSAIDS, an SMD of -1.04 (95% CI: -1.64, 0.43). The findings suggest that participants included in the study by Abramov[4] were clinically heterogeneous compared to other study populations included in the review. However, in both cases, we found significant statistical heterogeneity between studies.

Adverse Events

Four studies[2,4,20,21] provided data combined in a meta-analysis (Table 5b). We evaluated the relative risk (RR) of adverse events using data from 4 studies (n = 347) for postoperative complications of nausea and vomiting between the PNB and control arms. The RR was 0.42 (95% CI: 0.18, 0.99) in favor of PNB, with low levels of certainty. We found no significant statistical heterogeneity between studies.

Table 5b. Secondary Outcome Measures Reported as Categorical Outcomes

Study	Outcome		PNB (n, %)	Control (n, %)
Abramov 2005[4]	Additional boluses of hydromorphone (1 mg)		9 (18)	9 (18)
	Additional boluses of ketoralac (15 mg)		6 (12)	4 (8)
	Post-operative adverse effects of hydromorphone			
	Nausea/vomiting		2(4)	3(6)
	Itching		0 (0)	2(4)
	Respiratory distress		0 (0)	0 (0)
Ismail 2012[17]	Nausea		5 (7.69)	8 (12.31)
	Vomiting		2 (3.07)	4 (6.15)
	Urine retention		1 (1.53)	5 (7.69)
Rouholamin 2015[3]	Incidence of consumption of Morphine	Time point	PNB (n, %)	Control (n, %)
		1 hr - Yes	2 (6.9)	6 (20.7%)
		No	27 (93.1)	23 (79.3)
		2 hr (Yes)	6 (20.7)	7 (24.1)
		No	23 (79.3)	22 (75.9)
		4 hr (Yes)	6 (20.7)	15 (51.7)
		No	23 (79.3)	14 (48.3)
		6 hr (Yes)	16 (55.2)	14 (48.3)
		No	13 (44.8)	15 (51.7)
		12 hr (Yes)	11 (37.9)*	21 (72.4)*
		No	18 (62.1)	8 (27.6)
		24 hr (Yes)	6 (20.7)	10 (34.5)
		No	23 (79.3)	19 (65.5)
		48 hr (Yes)	3 (10.3)	5 (17.2)
		No	26 (89.7)	24 (82.8)
	Incidence of nausea with consumption of Metoclopramid, mg/kg	1 hr - Yes	1 (3.4)	3 (10.3)
		No	28 (96.6)	26 (89.7)
		2 hr (Yes)	0 (0.0)	2 (6.9)
		No	29 (100)	27 (93.1)
		4 hr (Yes)	1 (3.4)	1 (3.4)
		No	28 (96.6)	28 (96.6)
		6 hr (Yes)	0 (0.0)	0 (0.0)
		No	29 (100)	29 (100)
		12 hr (Yes)	1 (3.4)	3 (10.3)
		No	28 (96.6)	26 (89.7)
		24 hr (Yes)	0 (0.0)	2 (6.9)
		No	29 (100)	27 (93.1)
		48 hr (Yes)	0 (0.0)	1 (3.4)
		No	29 (100)	28 (96.6)
Khalil 2016[18]	Incidence of PONV		1 (3.6)*	12 (41.4)
	Patient satisfaction			
	Satisfied		20 (71.4)	8 (27.8)
	Partially Satisfied		4 (14.3)	2 (6.9)
	Unsatisfied		4 (14.3) **	19 (65.5)
	Surgeon satisfaction			
	Satisfied		23 (82.1)	10 (34.5)
	Partially Satisfied		1 (3.6)	0 (0.0)
	Unsatisfied		4 (14.3) **	19 (65.5)
	Requirement for additional intraoperative sedation in PNB group (Yes/No)			
	Stage of prolapse		Participants not requiring additional intraoperative sedation / patient requiring additional sedation	NA
	I		Yes - 9 (81.8) No - Propofol (50 mg) - 2 (18.0)	-
	II		Yes - 6 (60.0) No - Propofol (50 mg) - 4 (40.0)	-
	III		Yes - 0 (0.0) No - Propofol (50 mg) &sevoflurane (0.8) - 2 (40.0)	-
	III		Yes - 0 (0.0) No - Propofol (50 mg) &sevoflurane (2.5) - 3 (60.0)	-
	IV		Yes - 0 (0.0) No - Propofol (50 mg) &sevoflurane (2.5) - 2 (100.0)	-

PNB: Pudendal nerve block; n: number; %: percentage; mg: milligram; /: per; kg: kilogram; hr: hour; *p<0.05; **p<0.01; ***: p<0.001; PONV: post-operative nausea and vomiting; NA: Not applicable.

Length of Hospital Stay (in Hours)

Two studies[4,21] provided data (n = 232) for the length of stay that was combined in a meta-analysis. There were no significant differences between the mean length of hospital stay between the intervention (PNB) and control arms. The mean difference, MD, was -0.82 (95% CI: -5.34, 3.69) with no difference between the intervention or control groups. We found very low confidence in the evidence.

Return to Regular Activity (in Days)

We identified substantial heterogeneity between two studies[2,21] (n = 187) that evaluated return to regular activity and did not combine data. One study[2] reported MD of -0.96 (95% CI: -1.31, -0.61) in favor of PNB and the other[21] reported MD of -8.60 (95% CI: -10.16, -7.04).

Patient and Surgeon Satisfaction

We identified substantial heterogeneity between two studies[20,21] that evaluated patient and surgeon satisfaction. Two studies (n = 187)[20,21] reported improvement in patient satisfaction among patients who received PNB. One study (n = 57)[21] reported more surgeon satisfaction in favor of PNB.

Discussion

To our knowledge, this is the first systematic review and meta-analysis of published randomized controlled trials investigating pre-emptive analgesia for perineal or pelvic floor surgery. This systematic review aimed to evaluate the effect of pre-emptive analgesia using bupivacaine as a PNB on pain relief, additional analgesic requirements, adverse events, length of hospital stay and return to regular activity. The concept of pre-emptive analgesia in vaginal surgery aims to use local infiltration for the nerve block to reduce pain from the surgical wound in the form of a pudendal block or para-cervical nerve block. After vaginal reconstruction, postoperative pain is frequently defined as pain in the posterior vulva, perineum, and pelvic floor and infrequently as a perception of pelvic cramps.[3,18,19] Effective anesthesia to the vulva, lower vagina, and perineum is usually achieved by pudendal nerve blockade. The results of our meta-analysis showed small benefit on pain levels using PNB, although the evidence is of low quality and studies were clinically heterogeneous.

In this review, clinical trials on vaginal reconstructive surgeries evaluated pudendal block for pre-emptive pain control and showed the most consistent effect.[4,20,21] Pain scores were reduced for 24-36 hours by the analgesic effect of a pudendal block using bupivacaine. The study by Rouholamin et al, reported significant differences in pain within 48 hours when participants who underwent anterior and posterior vaginal wall repair received pudendal block compared with the control group.[2]

In the trial by Khalil et al, pudendal nerve block for postoperative pain management with nerve stimulator guide showed statistically and clinically relevant results on the first and second postoperative days (p = 0.005 and 0.004) among patients undergoing anterior and posterior vaginal wall repair.[21] The trial by Ismail et al, examined the effect of pre-emptive analgesia applied through different methods for posterior colpoperineorrhaphy. The authors used a pre-emptive nerve stimulator guided by bilateral pudendal nerve block, with better pain relief and reduced opioid use in the intervention group. The trial reported a shorter time to return to normal activities compared to the control group and higher patient as well as surgeon satisfaction.[20]

However, the trial by Abramov et al showed contradictory results.[4] This is probably due to the lower dose (50-75 mg bupivacaine) of local anesthetic compared to the other trials[2,20,21] that showed a better effect on pain reduction and postoperative analgesic requirements. This might have also resulted in an insufficient blockade of the nociceptive stimuli in the visceral afferent pain fibers during pelvic floor surgery. Furthermore, the study by Abramov[4] used a heterogeneous group that may underscore the change observed. Patients undergoing pelvic reconstructive surgery were included in the study. However, in the absence of hysterectomy, this approach may not be painful enough to produce a noticeable difference between groups.[4]

Overall, there was lower total analgesic consumption, shorter duration of recovery and higher surgeon and patient satisfaction in the pudendal block group.[20,21] However, the pharmacological interventions used to reduce postoperative opioid varied widely, and the certainty of the evidence was unclear. Furthermore, it is unclear what dose of analgesics or surgical technique would result insuperior outcomes. In the trial by Abramov,[4] the authors used hydromorphone and

ketorolac, while Rouholamin used Morphine consumption,[2] Ismail used pethidine, and paracetamol[20] and Khalil used Tramadol and Ketoprofen.[21] Therefore, we categorized these into sub-groups of opioids and NSAIDs and performed a sensitivity analysis to assess the overall effect size of both groups. We found low certainty of the evidence for effectiveness in favor of the PNB group compared to the control. Across all studies, postoperative nausea and vomiting were reportedly higher in the control group compared to the PNB group.[2,4,20,21] Patient satisfaction was reported to be significantly better in the PNB group than the control.[20,21] Surgeon satisfaction was reported as higher in the PNB group compared to the control, but only one RCT provided results for this outcome.[21] However, when we pooled this data in a meta-analysis, we did not find any significant difference in effect estimates. Similarly, for return to regular activity, a non-statistical improvement was reported by individual trials.[20,21] However, overall, there was significant heterogeneity between studies and no evidence of a difference in favor of a quicker return to regular activity between the PNB and control arms.

Pudendal nerve block in vaginal surgery has been used in a diversity of methods and clinical trials[15,31-33] to decrease postoperative pain and the use of postoperative opioids (Table 5a and 5b). Bupivacaine and ropivacaine are local anesthetics that have shown some evidence of analgesic effect in vaginal surgeries, although most of these studies describe bupivacaine as well.[3,17-19] In a review of over 11,000 cases by Moore,[13] the effect of 0.25%, 0.5%, and 0.75% bupivacaine was evaluated and found to be satisfactory in caudal, epidural and peripheral nerve block for obstetric, perineal and abdominal surgery. However, this review[13] only included case reports which are not designed to assess the effectiveness of medical interventions due to their propensity to bias.

Some of our results were similar to reports provided by previous studies[16,34] that investigated the use of PNB to reduce the postoperative pain scores and analgesic requirement but contradictory toother reports.[36-38] One trial[16] evaluated the analgesic effect of 0.25% bupivacaine on gluteal pain among patients who underwent sacrospinous ligament colpopexy. The authors[16] did not report reduced postoperative pain scores but founda significant reductionin pain medication requirement after surgery.[16] In another study, the authors assessed the effect of extended-release bupivacaine, also known as liposomal bupivacaine for reducing postoperative pain after robotic colpopexy and posterior repair.[37] The results showed no improvement in postoperative pain or decrease requirements for medications. However, this might be due to higher nerve involvement by robotic use.[37] On the contrary, Long et al, conducted a clinical trial among women undergoing vaginal surgery who were given 0.50% of bupivacaine using a paracervical approach as a pre-emptive analgesia. The authors reported statistically significant improvement in postoperative pain scores and the requirement for narcotics.[34]

Limitations

These results suggest that pre-emptive PNB might be beneficial for the management of postoperative pain and for reducing analgesic requirement, but its clinical importance remains unclear.[21] Expected disadvantages of pudendal nerve block are incomplete analgesia, systemic toxicity and hematoma formation.[2,4,20,21,34] However, these outcomes were not evaluated by studies included in this review and are poorly captured by non-observational study designs.

This study was designed using a comprehensive search strategy to reduce the possibility of publication bias. However, studies might have been missed that were not indexed in the databases searched for this review as an expert information scientist did not develop or peer-review the search strategy due to time and financial constraints. However, the search process was piloted using key references to ensure high specificity. The methodological quality of most studies was poor due to inadequate designs such as using opaque envelopes for allocation concealment and poor blinding techniques common in single center studies. This is important as inadequate allocation concealment during trial conduct has been shown to bias results, overestimating trial outcome.[24]

The evidence used to synthesize findings for this review were randomized controlled trials which represent the highest level of evidence. However, three[4,20,21] out of four[2,4,20,21] studies did not report complete study procedures or data in their published paper. Data were sometimes missing or inaccurate, which questions the validity of the findings used to synthesize evidence in this review. Due to the nature of studies identified and we could not explore the effect of other factors such as a subgroup analysis for the

indication of the type of approach; perineal or vaginal surgery; time of pain assessment. Although, we planned to perform sensitivity analyses to examine the effect of risk of bias on the results with adequate allocation concealment and sources of missing data; yet, there were insufficient trials to undertake these analyses.

Conclusion

This review found some evidence that pre-emptive pudendal blocks for perineal or vaginal surgeries might be beneficial for reducing postoperative pain, decreasing the use of opioids and NSAIDs. Further research is needed to confirm these conclusions using large, randomized controlled trials that assess report clinically relevant outcome measures.

Authors' Contributions

MR, DA, and AA developed, refined and designed the research topic. JT and MR developed the search strategy for the systematic review, carried out data extraction, quality assessment, data synthesis and interpretation of study results. DA and AA provided content area expertise during data synthesis of initial reports. MR, JT, DA, and AA contributed to critically appraising the evidence, writing and refining drafts until a final approved version was produced. All correspondence is to be directed to Jacqueline Y Thompson.

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Conflict of Interest

The authors declare no conflicts of interest.

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