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Efficacy of caudal neostigmine for postoperative pain relief: A systemic review and meta-analysis.

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Abstract

Caudal Epidural analgesia reduces the overall intraoperative Anesthetic requirement and facilitates rapid return of conscious state with stable hemodynamic condition. Different additives like, opioids, ketamine and clonidine have shown better pain management but brought about evitable complications. Addition of neostigmine improves pain management with minor postoperative complications. The purpose of this review was to compare caudal epidural neostigmine co-administered with bupivacaine and Bupivacaine alone.

Different databases were explored to identify controlled clinical trials comparing neostigmine co-administered with bupivacaine and bupivacaine alone. Seventeen controlled trails have been collected for eligibility assessment and eleven trials were incorporated for extraction of outcomes.

Eleven studies (838 participants) were included in this review. The mean difference of Postoperative analgesic duration was better in patients received neostigmine co-administered with bupivacaine when compared to bupivacaine alone (MD=3.29, 95% confidence interval (CI) 2.86 to 4.4, 4 trials, 193participants). There was significant association on postoperative analgesic consumption in 24 h when neostigmine group was compared with bupivacaine alone (SMD=-1.57, 95% confidence interval (CI) -2.14, 1.01, one trial, 63 participants).

Conclusion: Caudal epidural with neostigmine co-administered with bupivacaine is better as compared to caudal epidural with bupivacaine.

Keywords: Caudal epidural, Neostigmine, Bupivacaine, Postoperative analgesia.

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Introduction

Pain is the most distressful consequence of surgery with preventable complications in perioperative period [1,2]. However, expression of pain by younger children and even the method of pain assessment is more complex which makes children vulnerable to postoperative pain [3]. Studies showed that aggressive postoperative pain treatment in children with opioids and other analgesic alone were associated with many adverse effects [1,4-9].

Caudal epidural analgesia reduces the overall intraoperative anesthetic requirement and facilitates rapid return of conscious state with stable hemodynamic condition [1,4-7,9-15]. However, perioperative pain relief with single shot caudal block is inadequate which needs further administration of other analgesic drugs intravenously [7,9,13,14]. So far, different additives like, opioids, ketamine and clonidine have been used to enhance postoperative pain relief but associated with undesirable side effects [3-7,9,12-14].

Neostigmine provide pain relief by preventing the breakdown of acetylcholine in spinal cord mediated by muscarinic and cholinergic receptors with minimal postoperative side effects [4,5,8,14,16].

Some studies showed that administration of neostigmine and bupivacaine prolong postoperative analgesia in children having lower extremity surgeries [3-6,8-10,12,14], whereas, other study pointed out that neostigmine did not prolong the duration of postoperative analgesia [7,17].

Objective

To identify postoperative pain relief benefits of caudal neostigmine in children undergoing lower abdominal surgeries.

Studies in this Review

Study Design

Randomized controlled trials.

Population

All children scheduled for lower abdominal surgery.

Types of Intervention

Intervention*:* Children receiving caudal epidural Block with combined Neostigmine (2-4 µg/kg) and Bupivacaine (1 mg/kg).

Control: Children receiving caudal epidural Block with bupivacaine alone.

Outcomes

Main outcomes: The primary outcomes were analgesic duration and the total analgesic consumption in 24 h.

Secondary outcomes: The secondary outcomes were nausea and vomiting and change in hemodynamic parameters.

Criteria for Selection of Clinical Trials

Different databases were explored to identify controlled clinical trials comparing neostigmine co-administered with bupivacaine and bupivacaine alone. Full reports of all controlled clinical trials were searched without date and language restriction. Seventeen controlled trails have been collected for eligibility assessment and eleven trials were incorporated for extraction of outcomes.

Two review authors independently assess the eligibility assessment with checklist and disagreement was fixed by consensus. The method of eligibility assessment by each independent author was mentioned in Table 1 and the excluded Studies were described with reasons in Table 2.The study selection process was summarized using PRISMA chart (Figure 1).

Searching Strategy

Databases were searched for randomized clinical trials comparing neostigmine and bupivacaine without date and language restriction as shown below with medical subject heading (MeSH) terms of children, postoperative, pain, nausea and vomiting, caudal block were searched as follows:

Table 1. *Description of included studies*

Study	Year of Publication	Sample Size (N)	Intervention (neostigmine co-Administer With Bupivacaine	Control (bupivacaine)	Outcomes
Bhardwaj et al. [7]	2007	120	2, 3 and 4 µg/kg of Neostigmine with 1.875 mg/kg of bupivacaine in three groups	1.875 mg/kg of bupivacaine alone	Time to first analgesic, number of analgesic doses, sedation, vomiting
Dilek et al. [17]	2003	40	1 µg/kg of Neostigmine with 0.25% 0f 0.5 mg/kg bupivacaine	0.25% 0f 0.5 mg/kg bupivacaine alone	Duration of analgesia, pain score, nausea and vomiting
Emil et al. [10]	2015	134	1.5, 3 and 6 µg/kg of Neostigmine with 0.25% of 0.5 mg/kg of bupivacaine in three groups	0.25% of 0.5 mg/kg of bupivacaine alone	Duration of analgesia, analgesic consumption, pain score
Ataro et al. [8]	2014	86	2.5 µg/kg of Neostigmine with 0.25% of 1 mg/kg bupivacaine	0.25% of 1 mg/kg bupivacaine alone	Duration of analgesia, first rescue analgesic hors, vomiting, pain score
Kaushal et al. [6]	2008	90	2 and 5 µg/kg of Neostigmine with 0.25% of 1 mg/kg bupivacaine	0.25% of 1 mg/kg bupivacaine alone	Duration of analgesia, first rescue analgesic hour, vomiting, pain score
Abdulatif et al. [12]	2002	60	2 µg/kg, 2 µg/kg diluted with NS and 0.25% of 1mg/kg bupivacaine in two groups	0.25% of 1 mg/kg bupivacaine alone	Duration of analgesia, analgesic consumption, vomiting
Mrugesh et al. [1]	2016	75	1 and 2 µg/kg of Neostigmine with 0.25% of 1 mg/kg bupivacaine	0.25% of 1 mg/kg bupivacaine alone	Duration of analgesia, vomiting, number of rescue analgesics, pain scores
Tobin et al. [14]	2014	63	1.5 µg/kg of Neostigmine with 0.25% of 1 mg/kg bupivacaine	0.25% of 1 mg/kg bupivacaine alone	Time to first rescue analgesic, number of rescue analgesic, pain score, vomiting, fever
Rajesh et al. [3]	2004	80	2, 3 and 4 µg/kg of Neostigmine with 0.25% of 0.5 mg/kg bupivacaine in three groups	0.25% of 0.5 mg/kg bupivacaine alone	First rescue analgesics, analgesic consumption, vomiting
Anaesth et al. [9]	2005	40	2 µg/kg of Neostigmine with 0.25% of 1 mg/kg bupivacaine	0.25% of 1 mg/kg bupivacaine alone	Duration of analgesia, first analgesic hours nausea and vomiting
Sunanda et al. [4]	2013	50	2 µg/kg of Neostigmine with 0.125% of 2 mg/kg bupivacaine	0.125% of 2 mg/kg bupivacaine alone	Time to first rescue analgesic, number of rescue analgesic, pain score

Table 2. *Description of excluded studies*

Study	Year of Publication	Sample Size	Reasons for Exclusion
Gupta et al. [18]	2011	50	The intervention was bupivacaine. Used different doses of bupivacaine with fixed neostigmine dose
Kiran et al. [13]	2006	50	Different population group was used (adult). Neostigmine was compared with bupivacaine and lidocaine for epidural analgesia rather than bupivacaine alone
Sfyra et al. [5]	2007	50	Comparison was made with levobupivacaine
Sayed et al. [11]	2015	80	Randomization and blinding was done properly but the surgery was open heart surgery which was different from this population(children with lower extremity surgery)
Dilek et al. [17]	2003	44	Neostigmine was compared with ropivacaine, not bupivacaine
Kiran et al. [13]	2016	120	Neostigmine was compared with levobupivacaine, not bupivacaine

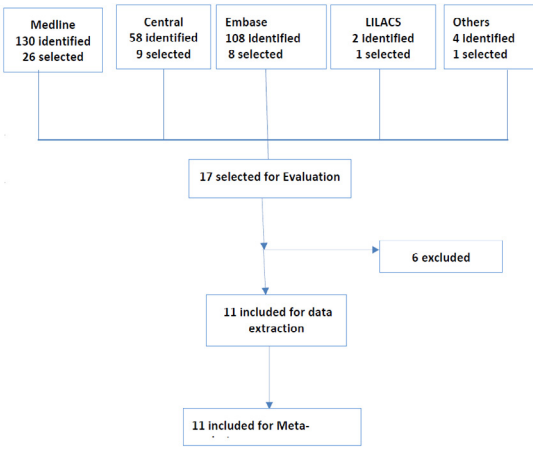


Figure 1. *PRISMA flow diagram*

1. Neostigmine
2. Bupivacaine
3. Caudal epidural
4. #1 and (#2 or #3)
5. Analgesia*
6. #4 and #5
7. Lower abdominal*
8. #6 and #7
9. Double blind
10. Random clinical trial
11. #8 and (#9 or #10)

Procedures of the Review

The principal author chose randomized clinical studies with full articles and no multiple publications. The two authors, SM and YA, check each study for eligibility as mentioned in methodology and the rest were excluded with reasons. The profile of included studies was assessed carefully with standard parameters as described in Table 3.

Statistical combination of data from two or more separate trials in a meta-analysis was decided based on the evaluation of the clinical and methodological heterogeneity. The inconsistency throughout trials was quantified with the I2 statistic, assuming a value more than 50% as a substantial heterogeneity.

The summary effect measure were risk ratio (RR) and odd ratio for dichotomous variables and mean Difference and standard deviation for continuous variables along with their corresponding 95% confidence intervals (CI). The meta-analysis was planned to be performed through a random-effects model and Mantel-Haenszel (M-H) statistical method, anticipating that trials would have different techniques and assuming that the actual true effects have a normal distribution.

The data Analysis was conducted using Review Manager (RevMan5.3, Cochrane Collaboration) and Comprehensive Meta-Analysis (CMA).This systematic review was carried out using the methods established by the Cochrane Handbook for Systematic Reviews of Interventions and we followed the recommendations and checklist items from the PRISMA Statement for Reporting Systematic Reviews and Meta-analysis.

Description of Studies

Three hundred and two trials were identified by searching strategy as shown in Figure 1. Seventeen studies were selected for evaluation with successive screening for eligibility. Finally, 11 studies with 838 participants were included for analysis and the rest were excluded with reasons (Table 2).

Eleven randomized clinical trials were published between 2002-2016. The age of included studies ranged from 1-15 years. Sample size varied from 40-134. General Anesthesia was given with nitrous oxide, oxygen and halothane in three studies [3,12,14]. In One study, general anesthesia was given with halothane with sleeping dose of thiopentone with laryngeal mask airway. Two studies

Table 3. *Risk of base table of included studies*

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Free of Other Bias	Jadad Scale		
							Randomization	Blinding	Withdrawal
Bhardwaj et al. [7]	A	B	A	A	A	A	2	2	0
Emil et al. [10]	B	B	A	A	A	A	2	1	0
Ataro et al. [8]	B	D	B	A	A	B	1	1	0
Kaushal et al. [6]	A	A	A	A	A	A	2	2	0
Emil et al. [10]	A	A	A	A	A	A	2	2	0
Mrugesh et al. [1]	B	B	D	A	A	A	1	1	0
Tobin et al. [14]	A	A	A	A	A	A	2	2	1
Rajesh et al. [3]	A	A	A	A	A	A	2	2	0
Anaesth et al. [9]	A	A	D	A	A	A	2	1	0
Sunanda et al. [4]	A	A	A	A	A	A	2	2	0
Dilek et al. [17]	A	A	A	A	A	A	2	2	5

combine fentanyl with propofol and halothane as induction agent [7,17]. The use of thiopental and succinylcholine for induction of anesthesia and intubation of the trachea was described in two studies. Two studies did not describe the method of induction [8,9]. Withdrawal of cases from the study were reported in two studies (Table 1) [14,17].

Results

Main Outcomes

As mentioned in methodology, postoperative analgesic duration and analgesic consumption were the primary outcomes. Four studies described mean postoperative analgesic duration and analgesic consumption with neostigmine compared with bupivacaine in two groups [4,9,14,17]. However, the five studies tried to identify the analgesic profile of neostigmine with different doses of neostigmine in 3-4 groups with a fixed bupivacaine dose. The ten studies presented the analgesic profile results in mean ± SD whereas only one study presented the analgesic profile results in median and range [8]. Ten studies concluded that caudal neostigmine co-administered with bupivacaine enhances the postoperative pain relief and also reduce requirement of rescue analgesic doses. In two studies, the postoperative analgesic profiles were similar between the groups and concluded that caudal neostigmine co-administered with bupivacaine didn't prolong postoperative analgesia [7,17].

Secondary Outcomes

Postoperative nausea and vomiting: Incidence of postoperative nausea and vomiting were studied in ten studies. From included studies, nine studies found out that groups received neostigmine had experience nausea and vomiting when compared to groups received bupivacaine alone [3,5-9,12,14,17]. One study showed no difference between the groups. Only one study did not study incidence of nausea and vomiting [10].

Sedation: Sedation was assessed with objective score based on eye opening in seven studies [3,5-7,9,12,17]. Six studies did not show any significant difference between the groups on sedation score [3,5,6,9,12,17]. Only one study found significant sedation score in patients received neostigmine [7]. Four studies didn't study sedation as an outcome [4,8,10,14,18].

Urinary retention: Urinary retention was reported in one study. There were two cases of urinary retention in patients who received bupivacaine alone as compared to neostigmine co-administered with bupivacaine which was only one [4]. The incidence of urinary retention was (5%) in neostigmine co-administered with bupivacaine compared with bupivacaine alone which was (2.5%).

Pruritis and flushing: Pruritis and flushing were reported in one study where there were three pruritus cases in neostigmine group as compared to bupivacaine alone (two cases). But flushing was higher in bupivacaine group as compared to neostigmine group, 5% and 7.5%, respectively [4].

Respiratory depression and hypotension: Respiratory depression and unstable hemodynamic condition were not reported in included studies.

Quantitative Data Synthesis

Neostigmine co-administered with bupivacaine and bupivacaine alone were compared as intervention and controlled respectively with postoperative analgesic profile as primary outcomes in children having caudal epidural block for lower extremity surgery.

Subgroup analysis of different groups with different doses of neostigmine with a fixed dose of bupivacaine showed that the standardized mean difference of postoperative analgesic duration was better in neostigmine group when compared to bupivacaine alone (SMD=4.28, 95% confidence interval (CI) 3.18, 5.37, three trials, 157 participants) (Figure 2). The postoperative analgesic duration was better in patients received Neostigmine co-administered with bupivacaine when compared to bupivacaine alone (MD=3.29; 95% confidence interval (CI) 2.82 to 3.76; 4 trials; 193 participants) (Figure 3).

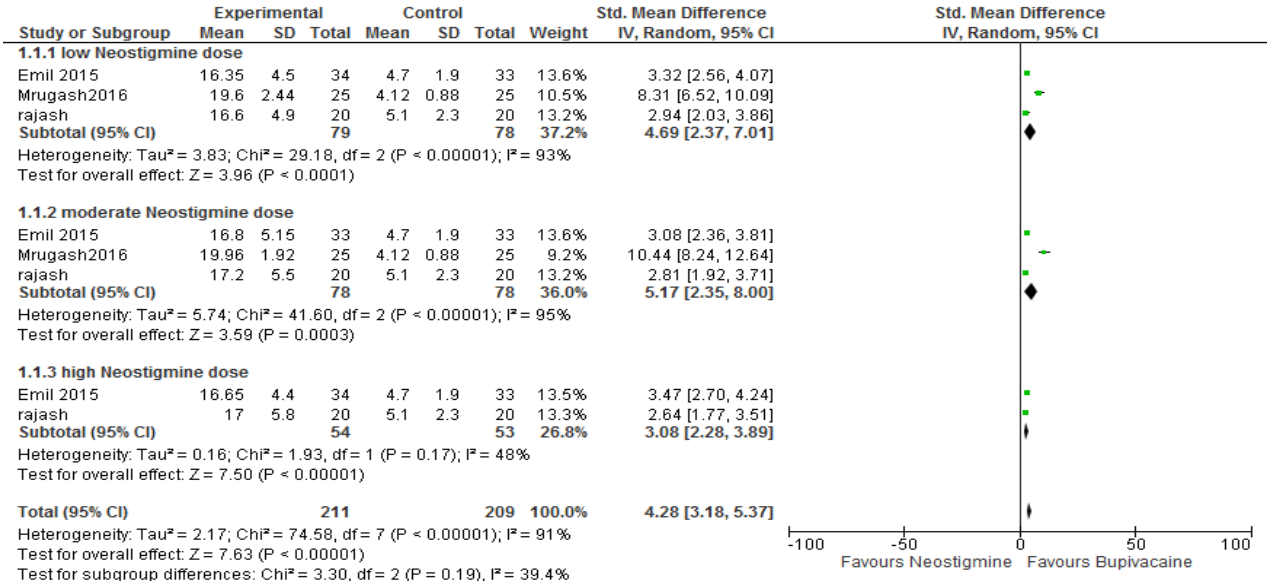
One study reported on postoperative analgesic consumption in 24 h and noted that there was significant association when neostigmine group was compared with bupivacaine alone (SMD=-1.57, 95% confidence interval (CI) -2.14, 1.01, one trial, 63 participants (Figure 4).

Post-operative nausea and vomiting was reported in three studies and there was no significant risk difference when neostigmine is compared with neostigmine alone (RD=0.06, 95% confidence interval (CI) -0.01, 0.14, 3 trials, 189 participants) (Figure 5).

Urinary retention, pruritus, sedation and flushing were reported in one study and did not show any significant risk difference when neostigmine was compared with bupivacaine alone (p>0.05) (Figure 5).

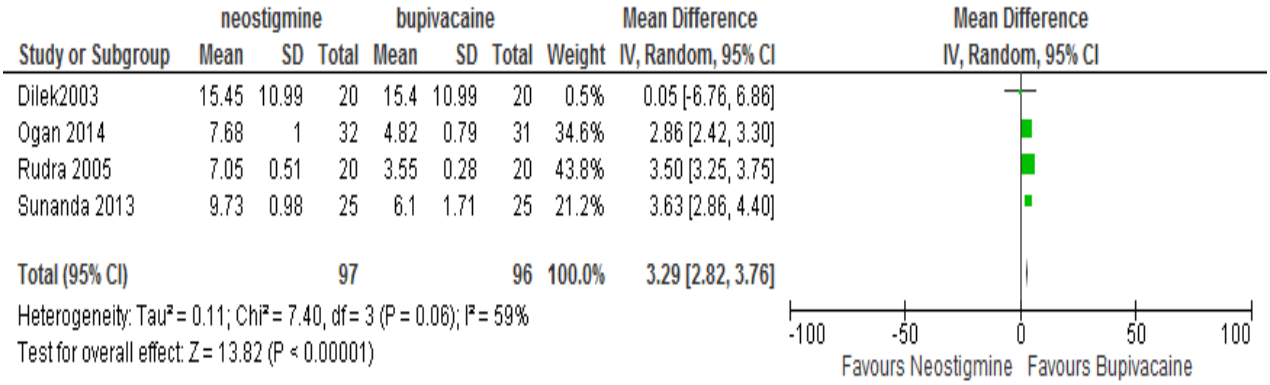
Discussion

This systemic review and meta-analysis tried to identify the benefit of caudal neostigmine administered with



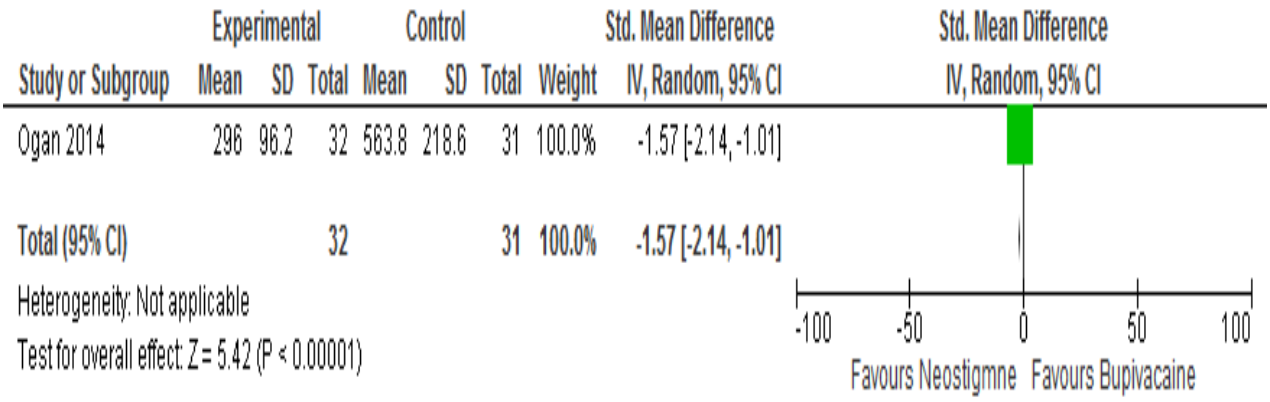
Total: The total number of participants in intervention (N) and control (B); Weight: Sample size contribution of the study relative to the pooled Sample size of the meta-analysis; IR: Inverse Variance; N: Neostigmine; B: Bupivacaine

Figure 2. *Forest plot for duration of postoperative analgesia comparing different doses of N vs. a fixed dose of B: individual trials and meta-analysis*



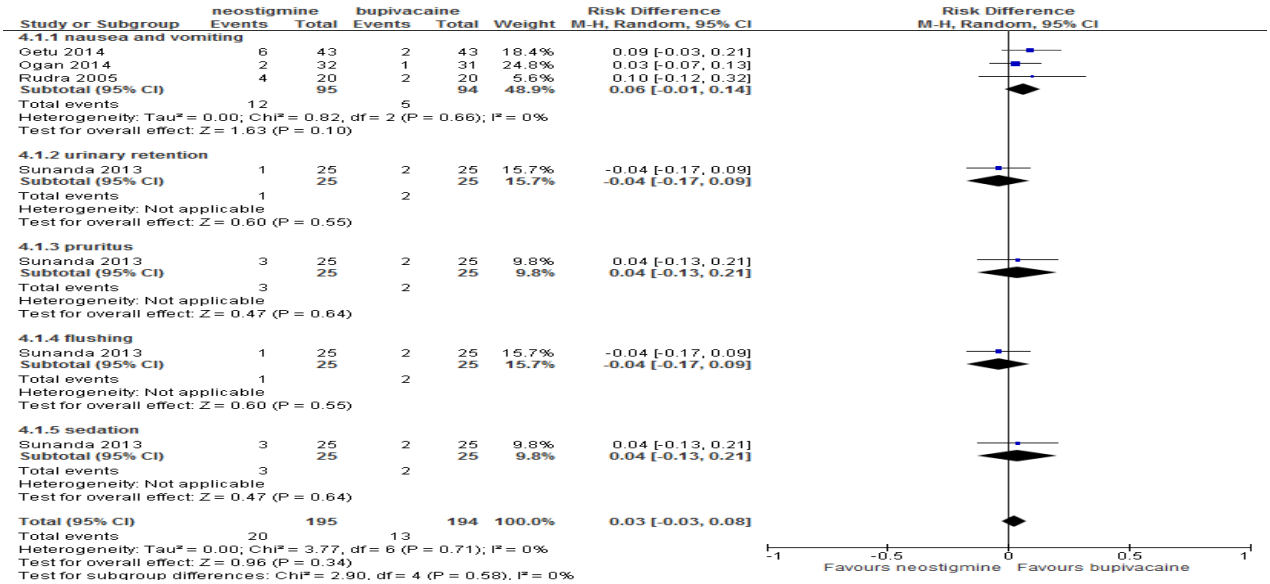
Total: The total number of participants in intervention (N) and control (B); Weight: Sample size contribution of the study relative to the pooled Sample size of the meta-analysis; IR: Inverse Variance; N: Neostigmine; B: Bupivacaine

Figure 3. *Forest plot for duration of postoperative analgesia (h) comparing N vs. B: individual trials and meta-analysis*



Total: the total number of participants in intervention (N) and control (B); Weight: Sample size contribution of the study relative to the pooled Sample size of the meta-analysis; IR: Inverse variance; N: Neostigmine; B: Bupivacaine

Figure 4. *Forest plot for postoperative analgesic consumption (mg) comparing N vs. B: Individual trials and meta-analysis*



Total: The total number of participants in intervention (N) and control (B); Weight: Sample size contribution of the study relative to the pooled Sample size of the meta-analysis; IR: Inverse Variance; N: Neostigmine; B: Bupivacaine

Figure 5. *Forest plot for postoperative complications comparing N vs. B: Individual trials and meta-analysis*

bupivacaine for postoperative pain relief in children undergoing lower extremity surgery.

Mortality was not reported in any of the included trials and this may reveal the relative safety of caudal epidural neostigmine with bupivacaine for perioperative pain management.

The review has shown that postoperative analgesic duration is better in patients receiving neostigmine along with bupivacaine compared to bupivacaine alone which is consistent with the majority of included randomized trials. However, two individual randomized trials did not show any significant difference on postoperative analgesic duration and this discrepancy might be due to small sample size or data collection bias.

Postoperative nausea and vomiting was higher in neostigmine co-administered with bupivacaine as compared to bupivacaine alone in individual trials. Nevertheless, the systemic review did not show any significant difference. This might be small sample size and low power which needs further review with large sample size.

The review also showed that requirement of rescue analgesia was less in children receiving caudal neostigmine co-administered with bupivacaine as compared to bupivacaine alone.

Despite insignificant difference, urinary retention was seen to be higher in cases received bupivacaine alone when compared to neostigmine co-administered with bupivacaine. This is because neostigmine has the advantage of contracting the detrusor muscles of bladder and voiding could easily be occurred unlike bupivacaine alone which relaxes the muscles of bladder helping for urination.

Sedation and pruritus were seen more often in cases received neostigmine co-administered with Bupivacaine as compared to bupivacaine alone, but the risk difference was not significant

Conclusion

Neostigmine co-administered with bupivacaine in caudal epidural enhances postoperative pain relief compared to bupivacaine alone. The postoperative rescue analgesic requirement is also lower in patients receiving neostigmine with bupivacaine compared to bupivacaine alone.

Declaration

Ethical approval and consent to participate the research has been approved by Dilla University institutional Board Review.

Availability of Data and Material

The Authors wish not share the data as per research and dissemination office.

Authors' Contribution

Semagn Mekonnen perceived and designed the study. Data extraction, analysis, interpretation of data and drafting the manuscript was accomplished by the two authors.

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This work was done by authors own resources.

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