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Clonidine and Morphine as Adjuvants for Caudal Anaesthesia in Children: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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Abstract

Objective: The aim of this systematic review and meta-analysis is to compare the outcomes of morphine vs. clonidine use as adjuvants in caudal anaesthesia. We are specifically focused on analgesic and side effect profiles.
Methods: We searched databases and trial registration sites and include here randomised controlled trials that compare the analgesic effects of caudal clonidine vs. morphine as adjuvants on postoperative pain. The risk ratio for evaluating pain scores, the need for rescue analgesia and all adverse effects were assessed. The i2 statistic was used to assess heterogeneity. We also assessed risk of bias with Cochrane's Collaboration tool. The quality of evidence was assessed with Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
Results: Four randomised controlled trials (including 166 patients) that evaluated the use of clonidine vs. morphine as adjuvants in caudal block were included in this systematic review and meta-analysis. The pooled estimate for postoperative analgesia revealed no statistically significant differences between the clonidine group compared to morphine group (MD=2.90; 95% CI 4.05 to 9.85; i2 93%). Significantly less postoperative nausea and vomiting were reported among the patients that received clonidine vs. those that were treated with morphine (RR 0.57, 95% CI −0.36 to −0.90, i2 26%). There were no statistically significant differences between the two groups in assessments that included urinary retention, pain scores or need for rescue analgesia at 24 hours.
Conclusion: Clonidine is just as effective as morphine when used an adjuvant to local anaesthetic for caudal block, and has a more desirable side effect profile, particularly with respect to postoperative nausea and vomiting.
Keywords: Anaesthesia, analgesia, caudal, children, clonidine, morphine

Introduction

Caudal anaesthesia is the most commonly used mode of analgesia for patients in the paediatric age group who are undergoing upper or lower abdominal surgeries. Caudal anaesthesia is safe and effective and can be used for both intraoperative and postoperative analgesia in this age cohort (1). Local anaesthetic agents have a short duration of action when used as single modalities; the addition of adjuvants to local anaesthetics prolongs the duration of postoperative analgesia (2). There are many adjuvants which can be used to prolong the duration of caudal analgesia, however, we have limited this analysis to a comparison between the effects of clonidine *vs.* morphine because, at this moment in time, these are the only two drugs currently approved by US Food and Drug Administration for epidural injection.

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Introduction of opioids, such as morphine, into the caudal space can be advantageous; in contrast to the effects of local anaesthetics, opioid drugs do not promote motor or sympathetic blockade. Opioids promote adjuvant analgesia via local action on spinal cord with limited systemic effects (3). Patients receiving this treatment should be monitored for at least 24 hours in a post-anaesthesia care unit (PACU) and observed on a frequent basis for level of consciousness and with sedation scores (4).

The analgesic effect of epidural clonidine relates to direct stimulation of α1 and α2 adrenoreceptors on the dorsal horn grey matter of the spinal cord, thereby inhibiting the release of nociceptive neurotransmitters (5). The most commonly encountered side effects of epidural clonidine are hypotension, bradycardia and sedation. The hypotensive effect of clonidine relates to its capacity to stimulate the α2 inhibitory neurons in the vasomotor centre of medulla, which are actions that lead to inhibition of norepinephrine release and central sympathetic outflow. Clonidine also decreases the electrical activity of preganglionic sympathetic nerves, stimulates central parasympathetic outflow and reduces sympathetic drive, thereby resulting in bradycardia (6). Clonidine also activates α2 receptors in locus coeruleus which suppresses the spontaneous discharge from the nucleus and activates inhibitory neurotransmitters including gamma aminobutyric acid. Clonidine also depresses CNS function and results in sedation (6, 7).

Although there are many published randomised controlled trials that have compared the efficacy of clonidine and morphine as adjuvants in caudal blockade, we were unable to identify any systematic reviews or meta-analyses on this subject. As such, the aims of this review and systematic meta-analysis are to compare the effects of adjuvant clonidine *vs.* morphine for prolongation of postoperative analgesia in paediatric surgical patients. Furthermore, we will review the findings that address pain scores and the need for rescue analgesia, as well as the incidence of side effects associated with these drugs including postoperative nausea and vomiting (PONV) and urinary retention.

Main Points:

- In this systematic review and meta-analysis, Morphine and Clonidine were compared as adjuvants in caudal anaesthesia.
- Four randomised controlled trials including 166 patients were pooled for various outcomes.
- We found that Clonidine is as effective as Morphine when used an adjuvant to local anaesthetic for caudal block.
- Clonidine has a more desirable side effect profile, particularly with respect to postoperative nausea and vomiting.
- There were no statistically significant differences between these 2 groups for urinary retention, pain scores or need for rescue analgesia at 24 hours.

Methods

We followed the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (8) and Cochrane database (9) in preparing this systematic review and a meta-analysis. Our study protocol and methods of analysis were pre-specified and are registered in PROSPERO, the international prospective register of systematic reviews, Registration no.: CRD42018104720.

Search strategy

We searched Pubmed Central, Cochrane Register of Controlled Trials, the Clinical Trial Registry and Google Scholar from the time of inception to August 2018 for Randomised Controlled Trials (RCTs) meeting our inclusion criteria and without any language restrictions. The reference list of received full articles were also searched. The following keywords were searched in the aforementioned databases: ('Caudal' OR 'Caudal analgesia' OR 'Caudal Block') AND ('Morphine'[Mesh] AND ('Clonidine'[Mesh] OR 'Randomised Control Trial' OR 'Trial') (Figure 1). The titles and abstracts of articles retrieved from this search strategy were examined by two independent authors and those deemed not relevant were excluded. In the cases of abstracts and titles that did not clarify eligibility, we attempted to retrieve full length articles. Full texts of articles identified as potentially relevant were reviewed. Articles fulfilling the inclusion criterion were assessed independently by two authors (SG and AS). Any discrepancy was resolved by communication with a third author (DG).

Our search focused on RCTs which included direct comparisons between clonidine and morphine as adjuvants in caudal anaesthesia for prolonging postoperative pain relief in paedi-

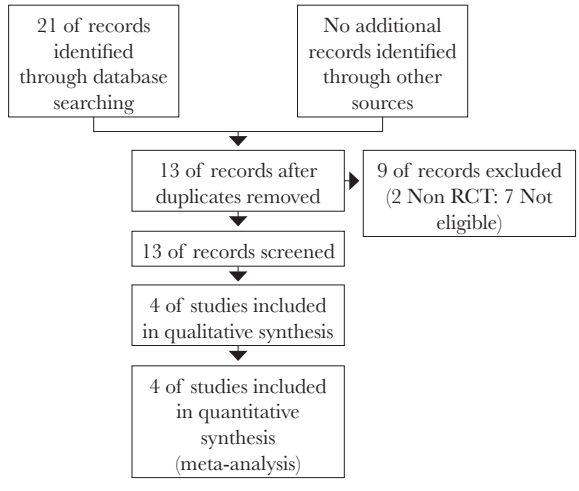

Figure 1. PRISMA flow diagram

atric patients. We excluded non-paediatric patients (age>18 years) and studies that did not measure 'duration of analgesia' as a primary outcome. We also excluded data from review articles, case reports, letter to editors, comments on published articles and data from animal studies (Figure 1).

Primary and secondary outcomes

The primary outcome was duration of analgesia. This outcome was measured as the time from administration of caudal block to the time at which rescue analgesia was needed. As expected, there was substantial heterogeneity in reporting of outcomes and in assessing of pain in paediatric patients; as in Vetter et al. (10), the time to administration of first rescue analgesia was accepted as a useful outcome measure. The secondary outcomes were postoperative pain scores and adverse effects including PONV and urinary retention.

Collection of data

The data were collected from the selected studies by three independent authors (SG, AS and NK); all findings were cross-checked. If the data included in a publication was not sufficiently detailed for our needs, we attempted to contact the authors by e-mail. The data extracted from the selected studies included all the basic information as well as the pre-specified outcomes of the RCTs. In order to simplify the meta-analysis, we approximated medians and interquartile ranges into means and corresponding standard deviations using methods as described in Cochrane library (9).

Assessment of risk of bias in independent studies

Two authors (SG and AS) independently assessed the risk of bias in the individual selected studies. In the case of any discrepancy, a common consensus was reached with the third author (DG).Trials with one or more domains of unclear or high risk of bias were designated as such.

Assessment of quality of evidence

We used Grading of Recommendations Assessment, Development and Evaluation (GRADEpro) methodology for assessing the overall quality of evidence for each outcome (11). The quality of evidence for each primary or secondary outcome was graded as high, moderate, low or very low.

Results

A summary of the four clinical trials included in this meta-analysis are listed in Table 1. The selected clinical trials include a total of 166 patients. GRADE summary of findings

Table 1. Characteristics of studies included in this meta-analysis

S.No	Authors/ Year	Age	Number of patients (clonidine/ morphine)	Surgery	LA used for caudal block	Amount of LA used (ml kg^{-1})	Scoring tool for pain	Definition of the duration of analgesia	Dose of Clonidine (mcs kg^{-1})	Dose of Morphine (mcs kg^{-1})
1	Luz (12) 1999	6 months to 6 years	18/18	Orchidopexy, Hernia repair, Circumcision	0.18% bupivacaine	1.5	OPS	Time from caudal block to first need of systemic analgesia	1	30
2	Vetter (10) 2007	6 months to 6 years	20/20	Ureteric re-implantation	0.2% ropivacaine	1	FLACC	Time from PACU admission to first postoperative FLACC pain score of 4 or more	2	50
3	Singh (3) 2011	1–6 years	25/25	Upper abdominal surgery	0.2% bupivacaine	1.25	FLACC	Time from caudal block to first need for systemic analgesia	2	30
4	Fernandez (5) 2011	1–10 years	20/20	Infraumbilicalurological and genital procedures	0.166% bupivacaine with epinephrine (1:600000)	1	FLACC	Time from caudal block to first need for systemic analgesia	1	20

LA: local anaesthetic drug; OPS: objective pain scale; FLACC: face, legs, activity, cry, consolability scale; PACU: post-anaesthesia care unit

in which the use of clonidine versus morphine is compared are included in Table 2.

Duration of analgesia

Two of the selected studies (3, 12) reported on the duration of analgesia; the other two studies (5, 10) included data that were not suitable for meta-analysis. Taken together, the two suitable studies included a total of 66 participants, 32 in the group that received clonidine with local anaesthetic and 34 in the group that were treated with morphine with local anaesthetic. The pooled estimate demonstrated no statistically significant differences between the two groups (MD=2.90, 95% CI 4.05 to 9.85, i2 93%, very low certainty evidence; Figure 2). The true observed heterogeneity between these studies was 94%; this finding indicates that results are significantly different among the studies. Variability between the studies was incorporated in the analysis by using a random effect rather than a fixed effect model. The data available were not sufficient for subgroup analysis. These results overall were graded as low certainty evidence.

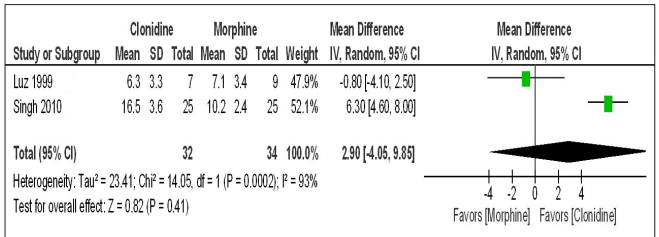

Figure 2. Forest plot for the primary outcome of duration of analgesia

Postoperative nausea and vomiting: All four studies (3, 5, 10, 12) provided data addressing PONV. In the clonidine group, 17/83 patients (20.5%) and the morphine group 30/83 patients (36.1%) reported this outcome. There were significantly fewer reports of PONV among the patients receiving clonidine group than among those receiving morphine (RR-0.57, 95% CI −0.36 to −0.90, i2, 26%, low certainty evidence; Figure 3a).

Urinary retention: The incidence of urinary retention was reported in only two (5, 12) of RCTs (total 76 patients). There were no statistically significant differences between the two

Table 2. Summary of findings

Clonidine compared to morphine in caudal analgesia in children: a systematic review and meta-analysis of randomised controlled trials

Patient or population: caudal analgesia in children: a systematic review and meta-analysis of randomised controlled trials

Intervention: Clonidine

Comparison: Morphine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Morphine	Risk with Clonidine				
Duration of analgesia	The mean duration of analgesia was 0	The mean duration of analgesia in the intervention group was 2.9 higher (4.05 lower to 9.85 higher)	-	66 (2 RCTs)	⊕○○○ VERY LOW	
PONV	361 per 1,000	220 per 1,000 (112 to 427)	RR 0.57 (0.36 to 0.90)	166 (4 RCTs)	⊕⊕○○ LOW	
Urinary Retention	53 per 1,000	11 per 1,000 (1 to 206)	RR 0.20 (0.01 to 3.92)	76 (2 RCTs)	⊕⊕○○ LOW	
Rescue Analgesia	379 per 1,000	607 per 1,000 (288 to 1,000)	RR 1.60 (0.76 to 3.36)	116 (3 RCTs)	⊕○○○ VERY LOW	
Pain Scores	-	-	-	116 (3 RCTs)	⊕⊕○○ LOW	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference; RR: Risk ratio; SMD: Standardised mean difference, RCT: randomised controlled trial, PONV: Postoperative nausea vomiting

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

treatment groups (RR0.20, 95% CI −0.01 to 3.92, heterogeneity, not applicable, low certainty evidence; Figure 3b).

Need for rescue analgesia: Three studies (5, 10, 12) with a total 116 participants contributed findings that addressed the need for rescue analgesia. We found no statistically significant differences regarding the need for rescue analgesia at 24 hours after surgery in the group that received clonidine compared to group that received morphine (RR 1.60, 95% CI 0.76 to 3.36, i2, 67%, very low certainty evidence) (Figure 4a).

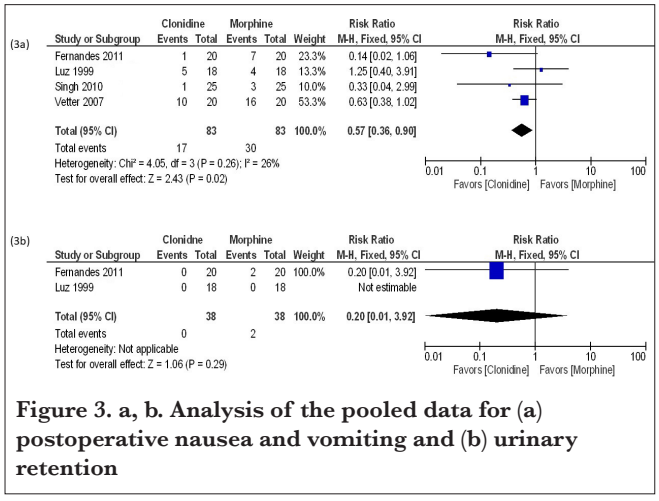

Figure 3. a, b. Analysis of the pooled data for (a) postoperative nausea and vomiting and (b) urinary retention

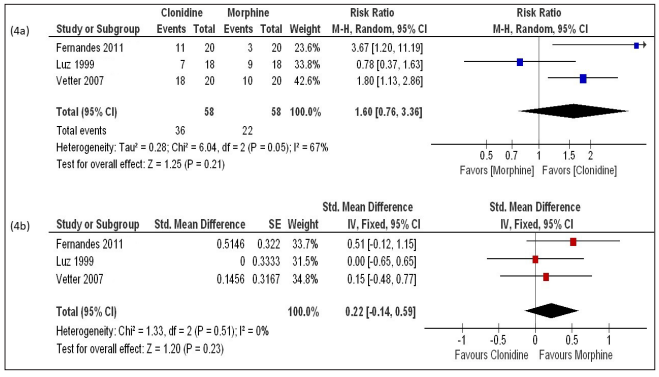

Figure 4. a, b. Analysis of the pooled data for (a) numbers of patients requiring postoperative rescue analgesia (b) postoperative pain scores

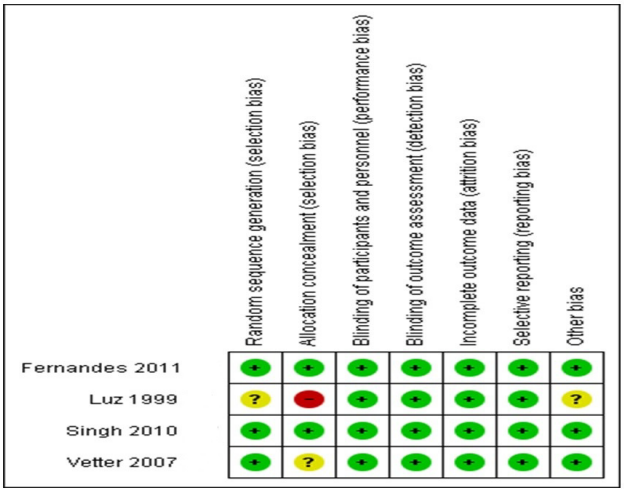

Figure 5. Risk of bias of the included trials

Pain scores: Pain was measured using various scoring tools; as such, we analysed the data using standardised mean difference (SMD) methods. Results from three studies (5, 10, 12) with 116 participants were consistent with one another; no statistically significant differences were observed between the treatment groups (SMD 0.22, 95% CI −0.14 to 0.59, i2 0%, low certainty evidence (Figure 4b). Of note, there were no pain scores included in the trial reported by Singh et al. (3). Objective Pain Scale (OPS) was used for pain assessment in Luz et al. (12) In the other two studies (5, 10) the paediatric Faces Legs Activity Cry Consolability (FLACC) pain scale was used to assess the need for rescue analgesia.

Risk of Bias: A tool from the Cochrane Collaboration was used to assess the risk of bias in each study. Risk of bias related to randomisation, allocation concealment, attrition and selective reporting, performance and detection bias was found to be low for most of the trials (Figure 5).

Publication bias: Publication bias is low. The current review includes only randomised trials and does not take into account any pilot or cohort studies; this was as per the inclusion criteria listed in the Methods.

Discussion

The mechanisms by which clonidine and morphine promote caudal anaesthesia are unique and distinct. Several mechanisms have been postulated for analgesic action of clonidine in this setting. Clonidine crosses the blood-brain barrier and combines with α2 adrenoceptors at spinal and supraspinal sites, thereby producing analgesia. Clonidine also elicits direct suppression of the spinal cord nociceptive neurons and suppresses peripheral sensory Aδ and C nerve fibre neurotransmission. Likewise, the pharmacokinetics of clonidine suggests that it may also function by inducing vasoconstriction through α 2b adrenoceptors which are located at the peripheral vascular smooth muscles (13).

Caudal clonidine in combination with bupivacaine has been used at different doses; increasing the dose of clonidine from 1 μg kg^{-1} to 2 μg kg^{-1} had no impact on its efficacy. Lee et al. (14) compared 0.25% bupivacaine at 1 mL kg^{-1} combined with either normal saline or clonidine at 2 μg kg^{-1}; mean duration of caudal analgesia was 5.2±1.2 hours and 9.8±2.1 hours, respectively ($p<0.0001$). Similarly, Singh et al. (15) reported that the mean duration of caudal analgesia with

0.75 mL kg^{-1} of 0.25% bupivacaine combined with 1 µg kg^{-1} of clonidine was significantly longer (629.06±286.32 min) than observed in response to any of the other study groups.

The analgesic effect of morphine can be attributed to its local action on opioid receptors at the spinal cord (16). Morphine is rapidly transferred from the epidural space to peripheral circulation and reaches a maximum concentration in plasma within 10 min after caudal block. Once in plasma, its half-life is approximately 2 hours, and the major pathway for its elimination is conjugation with glucuronic acid, forming morphine-6-glucuronide and morphine-3-glucuronide. The former metabolite is a potent analgesic compound in animal models (17). In humans, morphine-6-glucuronide produces similar pain relief, dysphoria and sedation with less respiratory depression than the parent morphine; morphine-3-glucuronide lacks significant activity (18). In children, adding morphine at 0.05 mg kg^{-1} to 0.125% bupivacaine improves the quality and prolongs postoperative analgesia after orchidopexy (3). However, in a retrospective study, 138 children received 0.07 mg kg^{-1} of morphine in a caudal block, with 11 patients (nearly 8%) reporting clinically significant hypoventilation (4).

Fernandes et al. (5) emphasised that the use of opioids in caudal epidurals in children has been questioned due to side effects, patient discomfort, delayed patient discharge and marginal efficacy. Use of morphine in caudal anaesthesia does not seem to be justified for minor procedures including those that are performed as day-case surgery; pain control for these procedures can typically be achieved with non-opioid agents. Use of morphine as a caudal adjuvant might be reserved for those procedures that require intensive postoperative analgesia with intravenous opioids.

Our meta-analysis included two randomised trials that focused on postoperative analgesia; the findings presented in the other two studies were not fully suitable for meta-analysis. Overall, the results revealed no statistically significant differences between the clonidine group vs. the morphine group for postoperative analgesia (MD=2.90, 95% CI 4.05 to 9.85, i2 93%, very low certainty evidence).The heterogeneity was 93%; the difference in the magnitude of the effects observed may be the result of different volumes and doses of local anaesthetic and drugs used. We inferred from this analysis that morphine as an adjuvant provided an equivalent duration of analgesia when compared to clonidine.

There was also no significant difference in need for rescue analgesia, as assessed by pain scores in three randomised trials (5, 10, 12). The report of Singh et al. (3) made no mention of pain scores or the need for rescue analgesia; the authors did not reply to our e-mail queries, and as such, we excluded this study from the assessment of these two criteria (Table 2). Luz et al. (12) used OPS as the pain score; rescue analgesia was administered when the value was greater than 4. The remaining trials (5, 10, 11) used FLACC for pain assessment; patients were given rescue analgesia when score was ≥4.

PONV was reported more frequently and with higher incidence in the group receiving morphine than in the clonidine group (p=0.02). Neuraxial opioids have been previously associated with a higher risk of PONV (19, 20); the 5-HT3 antagonist, ondansetron, is effective at reducing PONV secondary to epidural morphine (21). In the study presented by Fernandez et al. (5), the incidence of PONV was higher in morphine group (20 mcg kg^{-1}) and likewise in a comparable study by Wolf et al. (22), in which morphine was used at a dose of 50 mcg kg^{-1}. No prophylactic antiemetic therapy was used in these studies, which permits a better assessment of the risk of PONV. Vetter et al. (10) reported that a significantly larger number of children experienced PONV in response to morphine than in response to clonidine (80% vs. 50%; p=0.01), and noted the larger need for antiemetics in in the former group.

Urinary retention was comparable in the two groups. Fernandez et al. (5) reported urinary retention in two patients in morphine group and none in clonidine group. Urinary retention was relieved by simple measures.

Fernandez et al. (5) also reported that two patients in the morphine group developed pruritis but not treatment was necessary. Singh et al. (3) reported pruritis in 16% of the children in the morphine group vs. none in clonidine group, a finding that was statistically significant (p=0.03).

Vetter et al. (10) reported a higher incidence of pruritis in the morphine group as compared to clonidine group and was statistically significant (p=0.007).

Fernandez et al. (5) also reported no significant changes in hemodynamic parameters. This result was consistent with those reported in other studies (15, 23, 24). Luz et al. (12) also observed a slight decrease in mean arterial pressure, together with changes in heart and respiratory rates that were similar in both the groups. Singh et al. (3) observed no incidence of bradycardia or hypotension in either group.

Caudal morphine has been associated with respiratory depression, a finding that has been reported primarily in children less than 3 months of age and that has been associated with doses of caudal morphine varying from 40 to 70 µg kg^{1}. The study of Fernandez et al. (5) included no mention of respiratory depression, although the study was not sufficiently powered to detect this as a side effect. Similarly, Luz et al. (12) reported no evidence of respiratory depression after 30

μg kg^{-1} of morphine. Although this side effect is known to be dose dependent (4, 25), epidural morphine at doses as low as 40 μg kg^{-1} has resulted in respiratory depression (26, 27). Attia et al. (28) recommended continuous, mandatory respiratory monitoring for at least 22 hours in children who were treated with 50 μg kg^{-1} morphine as this has been associated with a decreased ventilatory response to CO_2. A literature search suggested that epidural clonidine, given in low dose (1–5 μg kg^{-1}) had no impact on respiratory function in children (23-25). Singh et al. (3) reported no incidence of respiratory depression in either group.

The report of Fernandez et al. (5) did not include sedation as a side effect. The time to emergence from anaesthesia was not prolonged in either the morphine or clonidine groups, results that suggest that the doses used in this study had no significant impact on sedation. Luz et al. (12) compared the analgesic efficacy, anaesthetic requirements and operation time and all outcomes were comparable in the two groups, although they noted that the longer recovery time observed among those in the clonidine group might be related to increased sedation (24, 29). Singh et al. (3) observed that the duration of sedation was significantly higher among those in the clonidine group as compared to the morphine group ($p<0.01$). Other studies suggest that there are no differences in the incidence of sedation in comparisons among agents used for caudal analgesia (15, 25).

Conclusion

Clonidine is equivalent to morphine as an analgesic when each is used as an adjuvant to local anaesthetic for caudal block. Clonidine has a more desirable side effect profile, particularly in terms of PONV.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.G., A.S.; Design – S.G., A.S.; Supervision – N.K., V.V.; Resources – D.G.; Materials – A.G., R.S.; Data Collection and/or Processing – S.G., A.S.; Analysis and/or Interpretation – R.K., S.S.; Literature Search – A.S., V.V.; Writing Manuscript – S.G., A.S., V.V.; Critical Review – A.G., V.V., R.S.; Other – N.K., D.G., A.G., R.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

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