Original Article

Postoperative analgesia in children when using clonidine or fentanyl with ropivacaine given caudally

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Abstract

Background: The aim of the study was to compare the efficacy of clonidine and fentanyl as an additive to ropivacaine given via single shot caudal epidural in pediatric patients for postoperative pain relief.

Materials and Methods: In the present double blind study, 90 children of ASA-I-II aged 3-8 years scheduled for infraumblical surgical procedures were randomly allocated to two groups to receive either ropivacaine 0.25% 1 ml/kg + clonidine 2 µg/kg (group I) or ropivacaine 0.25% 1 µl/kg + fentanyl 1 µg/kg (group II). Caudal block was performed after the induction of general anesthesia. Postoperatively patients were observed for analgesia, sedation, hemodynamics, and side effects/complications.

Results: Both the groups were similar with respect to patient and various block characteristics. The analgesic properties and hemodynamics were also comparable in both groups ($P > 0.05$). Side effects such as respiratory depression, vomiting bradycardia were significantly less in group I than group II ($P < 0.05$) ensuing more patient comfort.

Conclusions: The analgesic properties of clonidine and fentanyl as additives to ropivacaine in single shot caudal epidural in children are comparable but clonidine offers a more favorable side effect profile. The use of clonidine as additive to ropivacaine in caudal epidural is superior choice to fentanyl because of lack of unwanted side effects and increased patient comfort.

Key words: Caudal epidural, clonidine, fentanyl, pediatric, postoperative analgesia, ropivacaine

Introduction

In pediatric patients, though general anesthesia is the commonly used technique, regional anesthesia as analgesic adjunct is used for intraoperative as well as postoperative pain relief. For abdominal and lower limb surgeries, caudal epidural is commonly used as it is a safe, reliable, and easy to administer technique.[1] Caudal epidural is a simple technique allowing rapid recovery from anesthesia with effective postoperative analgesia.[2] In comparison to bupivacaine, ropivacaine is known to have lesser cardiotoxicity[3-5] and motor blockade,[6,7] with similar pain relief[6,7] at equivalent analgesic doses. It is considered to be a better agent for caudal epidural analgesia in children.[3,8] The duration of block is shorter even with longer acting local anesthetic agents like bupivacaine or ropivacaine because the local anesthetic spreads easily in children. The addition of an adjuvant not only increases the effectiveness of a local anesthetic by prolonging and intensifying the sensory blockade but also causes reduction in dose of local anesthetic agents. Many adjuvants can be used to achieve prolongation of sensory blockade, e.g., epinephrine, opioids ketamine, neostigmine. Epinephrine can cause serious side effects if inadvertently injected intravenously or intrathecally. Opioids can be given but they can cause confusion, itching, nausea, vomiting, and respiratory depression.[9-11] Ketamine can cause neurotoxicity if accidentally injected in cerebrospinal fluid (CSF).[12] Neostigmine is associated with a higher incidence of vomiting.[13]

Clonidine was introduced in the market as an antihypertensive agent but in recent times it is also used for sedation, as premedication, and as an adjuvant analgesic.[13,14] Clonidine is a centrally acting selective alpha-2 agonist. It has mild alpha-1 agonist activity (alpha-2: alpha-1.22:1)[15] When given epidurally, Clonidine exerts analgesic action by stimulating the descending noraderenergic medullospinal pathways and inhibiting the release of nociceptive neurotransmitters in the dorsal horn of spinal cord.[16,17] Neuraxial administration of

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Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.81842

clonidine is preferred as it has intense analgesic effect because of it's spinal site of action.[18,19]

Epidural fentanyl has been widely used as analgesic adjuvant. Its main site of action is the substantia gelatinosa on the dorsal horn of spinal cord. It blocks fibers carrying nociceptive impulses both pre and post synaptically.[20]

We planned this randomized, prospective, double blind study to compare the analgesic properties of clonidine and fentanyl as analgesic additive in caudal epidural with ropivacaine in children.

Materials and Methods

After obtaining approval from institutional ethical committee and written informed consent from parents, 90 ASA I-II patients aged 3–8 years, weighing 5–20 kg, scheduled to undergo infraumblical surgical procedures such as hernia repair, orchidopexy, hypospadias, and urethroplasty were enrolled in the study [Power of the study was 70% (α error = 10%) calculated using PS power and sample size calculation version 2.1.30 softwarecheked ok). Children with local infection of the caudal area, history of allergic reactions to local anesthetics, bleeding diasthesis, preexisting neurological or spinal diseases, mental retardation, neuromuscular disorders were excluded from the study.

The study design of the trial was prospective, double blind, randomized, and clinically controlled. Patients were premedicated with midazolam 0.4mg/kg orally 30-40 min before surgery. All patients were given general anesthesia. Anesthesia was induced with oxygen, nitrous oxide 60% and halothane (2%-3%) through Jackson-Ree's modification of Ayre's T piece with appropriate size face mask and standard monitoring (heart rate, non invasive blood pressure and pulse oximetry). After induction of anesthesia intravenous cannula was placed and Laryngeal Mask Airway (LMA) of appropriate size introduced. Anesthesia was maintained with O2-N2O (1:2) and isoflurane (2%-3%) with respiration assisted manually with fresh gas flow of 2-3 L/min. Patients were randomly allocated into one of the 2 groups by opening sealed envelope. Group I received ropivacaine 0.25% 1 ml/kg with clonidine 2 μg/kg; while Group II received ropivacaine 0.25% 1 ml/kg with fentanyl 1 μg/kg. For each patient two different syringes were prepared by an anesthesiologist not involved in the study. One syringe contained ropivacaine and the other contained 0.1 ml/kg of either clonidine or fentanyl. Normal saline was added to clonidine or fentanyl to achieve a total volume of 0.1 ml/kg. Caudal block was given under full asepsis with 23G short bevel hypodermic needle in left lateral position. Patient was turned supine after administration of the drug. The anesthetist in-charge of the patient was completely unaware of the content of syringes. After closure of skin incision, nitrous oxide and isoflurane were discontinued, the LMA was removed and patients were shifted to the post anesthesia care unit (PACU) when fully awake, breathing room air.

Heart rate (HR), mean arterial pressure (MAP) and oxygen saturation (SpO_2) were recorded before induction of anaesthesia, after induction but before caudal anaesthesia, 5 min after caudal anesthesia and every 5 min thereafter till the patient was shifted to PACU. During intraoperative period adequacy of analgesia was gauged by hemodynamic stability. An increase or decrease in the HR > 15% from the baseline values was considered as tachycardia or bradycardia. Similarly, an increase or decrease in MAP >15% was considered as hypertension or hypotension. Absence of rise of HR or MAP of more than 15% compared with baseline values recorded just before surgical incision was considered as adequate analgesia. An increase in HR or MAP (>15%), 15 min after administration of caudal anesthesia was defined as failure of analgesia. If HR, MAP increased 45 min after surgical incision it was considered as inadequate analgesia. Patients with failure of caudal analgesia or inadequate analgesia were given fentanyl 1 μg/kg intravenously. Patients, in whom caudal anesthesia failed or inadequate analgesia was present, were excluded from study. Time from caudal block to skin incision, duration of surgery, duration of general anesthesia, and time to removal of LMA after discontinuation of inhalational anesthetic agent was recorded.

In PACU analgesia, sedation, HR, MAP, SPO_2, and side effects were monitored by blinded observer every 30 min for 6 hours, and thereafter hourly till 12 hrs after caudal block. Pain was assessed using Hannallah Pain Scale [Table 1].[8] If patients had score of >4 on at least 2 occasions or showed obvious signs of pain they were given oral paracetamol 10 mg/kg. The duration of postoperative analgesia was defined as time interval between caudal anesthesia and first complaint of pain. Assessment of sedation was done 30 min, 1 hour, 2 hours, and 4 hours after surgery using 3 point sedation score [Table 2].

SpO_2 was monitored continuously and SpO_2<95% was defined as desaturation. Assessment of duration of motor blockade was done by noting the time from caudal block to spontaneous movements of leg by patient. Time of micturition was defined as time from administration of caudal block to spontaneous voiding of urine. Side effects like nausea, vomiting, respiratory depression, pruritus hypotension, and bradycardia were also noted. Statistical analysis was done

Table 1: Hannallah pain scale

Observation	Criteria	Points
Arterial Pressure	+10% Pre op	0
	>20% Pre op	1
	>30% Pre op	2
Crying	No crying	0
	Crying responded to tender loving care (TLC)	1
	Crying not responding to TLC	2
Movement	None	0
	Restless	1
	Thrusting	2
Agitation	Asleep/calm	0
	Mild	1
	Hysterical	2
Posture	No special Posture	0
	Flexing Legs and Thighs	1
	Holding groin	2
Complains of Pain	Asleep/states no pain	0
	Cannot localize	1
	Can localize pain	2

Table 3: Demographic and clinical data (mean ± SD or range)

	Group I *n* = 45	Group II *n* = 45	
Age (months)	61 (36-84)	49 (40-94)	NS
Weight (kg)	18 ± 6.2	15 ± 7.2	NS
Sex (M/F) Ratio	16:14	15:15	NS
Type of Surgery			
Hernia repair	22	21	
Hypospadias	10	10	
Orchidopexy	9	9	
Urethroplasty	4	5	
Duration of general anesthesia (min)	102.01 ± 9.70	103.10 ± 5.12	T = 0.70, df = 88, *P* = 0.485(NS)
Duration of Surgery (min)	46.22 ± 5.22	48.22 ± 6.12	T = 1.97, df = 88, *P* = 0.0988(NS)
Time from caudal block to incision (min)	22 ± 6.7	20 ± 9.1	T = 1.2, df = 88, *P* = 0.228 (NS)
Time to removal of LMA	5.46 ± 2.22	5.54 ± 2.68	T = 0.15, df = 88, *P* = 0.877(NS)
HR before induction (beats/min)	113.25 ± 12.25	117.11 ± 11.68	T = 1.53, df = 88, *P* = 0.129 (NS)
MAP before induction (mmHg)	73.25 ± 10.26	72.90 ± 12.65	T = 0.14, df = 88, *P* = 0.885(NS)

df = Degree of freedom; NS = Not significant

using student t-test and chi-square test. $P < 0.05$ was regarded as statistically significant.

Results

Ninety pediatric patients, 45 in group I and 45 in group II were studied. Both the groups were comparable with regard to mean age, weight, gender, duration of general anesthesia, duration of surgery, time from caudal block to incision, and time to removal of LMA after discontinuation of volatile anesthetic agent [Table 3].

Table 2: Sedation score

Sedation score	
1	asleep, not arousable by verbal contact
2	asleep, arousable by verbal contact
3	drowsy not sleeping
4	alert/awake

Table 4: Intraoperative vitals (mean value ± S.D)

	Group I *n* = 45	Group II *n* = 45	
HR before induction (beats/min)	113.25 ± 12.25	117.11 ± 11.68	T = 1.53, DF = 88, *P* = 0.129 (NS)
Intra op HR	96.22 ± 6.81	97.42 ± 7.01	T = 0.82, DF = 88, *P* = 0.41
Postop HR	107.42 ± 8.22	109.22 ± 6.92	T = 1.07, DF = 88, *P* = 0.287
MAP before induction (mmHg)	73.25 ± 10.26	72.90 ± 12.65	T = 0.14, DF = 88, *P* = 0.885(NS)
Intraop MAP	68.24 ± 10.21	67.14 ± 9.68	T = 0.52, DF = 88, *P* = 0.60
Postop MAP	69.84 ± 11.20	68.72 ± 11.22	T = 0.47, DF = 88, *P* = 0.63
Pre op SPO_2	97 ± 3.0	97 ± 2.5	T = 0.00, DF = 88, *P* = 1.0
Intraop SPO_2	97 ± 2.24	97 ± 2.26	T = 0.00, DF = 88, *P* = 1.000
Postop SPO2	97 ± 2.76	96 ± 3.02	T = 1.84, DF = 88, *P* = 0.104

df = Degree of freedom, NS = Not significant

The MAP, HR, and SpO_2 at induction, intraoperatively and postoperatively, when compared between the two groups using student t-test, yielded *P values* > 0.05, which were not significant [Table 4]. MAP decreased in both groups by 10–15% during anesthesia and increased by 5–15% during recovery but the changes were not significant ($P > 0.05$). HR also decreased during anesthesia followed by an increase in postop period in both the groups ($P > 0.05$). No patient in either group had a drop in HR to less than 80 beats per minute.

Mean duration of surgery was 46.22 ± 5.22 in group I and 48.22 ± 6.12 in group II ($P > 0.05$). Surgical analgesia in both the groups was found to be adequate. No patient in either group required intraoperative rescue analgesia. No patient in either group required analgesia until 6 hours postoperatively. After 6 hours, however, pain score was significantly higher in group II than group I ($P < 0.05$) [Table 5]. The mean duration of analgesia was longer in group I than in group II, but the difference was not statistically significant ($P > 0.05$). The dose of paracetamol required was higher in group II than group I but this was also not statistically significant ($P > 0.05$) [Table 6]. The postoperative sedation score were similar in both groups [Table 7].

The complications/side effects seen in the two groups are

Table 5: Post operative pain scoring (mean value ± S.D)

Hour	Group I	Group II	
0	0.24 ± 0.2	0.26 ± 0.5	T = 0.25, df = 88, *P* = 0.803
1	0.8 ± 0.7	0.90 ± 0.8	T = 0.63, df = 88, *P* = 0.529
2	1.01 ± 0.2	1.08 ± 0.02	T = 2.34, df = 88, *P* = 0.021
3	1.20 ± 0.1	1.36 ± 0.80	T = 1.34, df = 88, *P* = 0.186
4	1.28 ± 0.4	1.40 ± 0.6	T = 1.12, df = 88, *P* = 0.267
5	1.36 ± 0.02	1.42 ± 0.7	T = 0.57, df = 88, *P* = 0.566
6	1.62 ± 0.6	1.68 ± 0.9	T = 0.37, df = 88, *P* = 0.710
7	2.60 ± 0.8	3.02 ± 0.2	T = 2.82, df = 88, *P* = 0.0059 (s)
8	3.98 ± 0.9	4.88 ± 0.60	T = 5.58, df = 88, *P* = 0.000

df = Degree of freedom; NS = Not significant; S = Significant

Table 7: Postoperative sedation score in both groups

Group I	Group II	χ^2
None	None	$\chi^2 = 1.11$
3	1	df = 2
9	9	*P* = 0.575
18	20	

shown as [Table 8]. Residual motor blockade on arrival in PACU and time to complete regression of motor block were similar in both groups. SpO_2 decreased to 91% in 5 patients in group II in first hour in PACU. Eight patients of group II suffered from vomiting and bradycardia occurred in 3 patients in group II. These complications (respiratory depression, vomiting, and bradycardia) were not observed in group I and difference between two was statistically significant ($P < 0.05$). No patient in either group had urinary retention and pruritus.

Discussion

Caudal epidural anesthesia is a simple, frequently used technique, which provides very effective analgesia intra- and postoperatively in pediatric patients undergoing infraumbilical surgeries. The search for the ideal combination of drugs for caudal anesthesia in pediatric patients is on. Efforts are being made to find relatively safer drugs with minimal side effects. Ropivacaine is a local anesthetic with better safety margin and reduced risk of cardiac toxicity.[3-6] Separation of sensory and motor effects is more with ropivacaine than with bupivacaine.[7] Ropivacaine is more commonly used for caudal blocks in pediatric patients.[8] This study demonstrates that in a single shot caudal block with clonidine or fentanyl added to ropivacaine prolongs analgesia.

Bosenberg A[21] *et al.* demonstrated that ropivacaine 0.2% provided satisfactory postoperative pain relief, while 0.1% was less effective and 0.3% was associated with higher incidence of motor block with minimal improvement in pain relief. We designed this study keeping this in mind. Previous reports[22-24]

Table 6: Postoperative clinical data (mean value ± S.D)

	Group I	Group II	
First administration of paracetamol in PACU (hr)	7.0 ± 2.0	6.0 ± 3.4	T = 1.70, df = 88, *P* = 0.092
Dose of paracetamol (mg)	92 ± 64	106 ± 70	T = 0.99, df = 88, *P* = 0.324

df = Degree of freedom; NS = Not significant

Table 8: Complication/Side effects

Complication/Side effects	Group I *n* = 45	Group II *n* = 45	χ^2
Nausea/vomiting	0	8	$\chi^2 = 13.14$ df = 4 *P* = 0.0105
Respiratory depression SPO_2< 95%	0	5	
Bradycardia	0	3	
Hypotension	1	2	
Dry mouth	2	0	
Residual motor blockade	6	5	
Time to complete regression of residual motor blockade	240 ± 30	210 ± 30	

df = Degree of freedom; NS = Not significant; S = Significant

demonstrated that ropivacaine produces vasoconstriction in contrast to vasodilatation produced by bupivacaine, so we hypothesized that using additive with ropivacaine will provide more analgesic advantage compared to bupivacaine.

Various drugs were tried to prolong the duration of analgesia with minimal side effects because the mean duration of analgesia provided with even longer acting local anesthesia is limited. Fentanyl, a lipophillic opioid is very commonly used as an additive to local anesthetics in children. Although there is no debate about its beneficial effects, side effects like respiratory depression, nausea, and vomiting are common.[25,26]

Clonidine an α_2 agonist has also been used as additive to local anesthetics, e.g., bupivacaine,[27,28] mepivacaine,[29] lignocaine.[30] Its addition increases duration and improves quality of analgesia provided by single shot caudal anesthesia. Clonidine when used extradurally provides analgesia by nonopioid spinal effects. Clonidine is devoid of opioid side effects but may produce excessive sedation, hypotension, and bradycardia in adults.[17]

In the present study, addition of clonidine and fentanyl to ropivacaine was found to be effective in providing effective intraoperative and postoperative analgesia. The patients in group II required analgesia supplementation slightly earlier in the postoperative period as compared to group I, but this difference was not statistically significant. Respiratory depression is an expected but unwanted side effect of extradural opioid;[31] it has also been noticed in adult patients who

received clonidine 300 μg extradurally.[32] Many previous studies have however not reported respiratory depression after caudal administration of fentanyl[25,26,33] or clonidine[27,28,30,34] in pediatric patients. In our study, a transient decrease of oxygen saturation to 91% was observed in 5 cases of group II, while no patient of group I suffered hemoglobin desaturation ($P = 0.0105$). A sedative effect was observed after epidural clonidine in adults[32] and to a lesser degree in children.[27,28] In our study, time taken to removal of LMA and sedation score was not significantly different in both the groups ($P = 0.877$, $P = 0.575$). In group I, 3 patients and 1 patient of group II had sedation of 2 but this was not significant ($P = 0.575$)

Hypotension and bradycardia are expected side effect of extradural clonidine in adults[17] and depend on the dose administered, however in children the hemodynamic effects of extradural clonidine are less pronounced than in adults.[27,28,34] In the present study, we observed a similar hemodynamic profile in both groups intraoperatively as well as postoperatively. No patient of either group had hypotension. No patient of group I suffered from bradycardia, while 3 patients of group II had bradycardia but this was not significant. No patient of either group had a fall in HR to less than 80 beats per minute.

Eight patients out of 45 had vomiting in group II, but no patient of group I had vomiting in postoperative period. The extradural opioids are well known for their emetic effect while clonidine has anti-emetic properties when administered orally[35] or intravenously.[36] Presence of lesser side effects may be an argument for the use of clonidine rather than fentanyl as an adjunct to local anesthetics when prolongation of analgesia is required.

Conclusion

The addition of clonidine or fentanyl to ropivacaine prolongs the duration of analgesia after single shot caudal epidural anesthesia. Clonidine offers some advantages over fentanyl as it does not produce clinically and statistically significant undesirable side effects like respiratory depression, vomiting and bradycardia. We recommend the use of clonidine as additive to ropivacaine in caudal anesthesia, in children, as it has a more favorable side effect profile than fentanyl.

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Source of Support: Nil, **Conflict of Interest:** None declared.