ORIGINAL ARTICLE

Bali Journal of Anesthesiology (*BJOA*) 2018, Volume 2, Number 3: 65-71
E-ISSN: 2549-2276

Published by DiscoverSys

EFFECT OF CLONIDINE ADDED TO CAUDAL ROPIVACAINE IN PEDIATRIC INFRAUMBILICAL SURGERIES

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ABSTRACT

Background: Caudal epidural block is the most popular regional anesthesia technique in pediatrics. Several agents are required as an adjuvant with a local anesthetic to prolong the duration of caudal analgesia by single shot technique in children. The aim of this study was to compare the efficacy of clonidine with ropivacaine versus ropivacaine alone for caudal analgesia in children undergoing infraumbilical surgeries under general anesthesia.

Methods: Sixty patients of ASA grade I – II between the ages of 1-12 years, of either sex, undergoing infraumbilical surgeries under general anesthesia were included randomly into two groups: Control group (Group A) ropivacaine 0.2% (1ml/kg) with maximum volume 12 ml and clonidine group (Group B) ropivacaine 0.2% (1ml/kg) with clonidine 1µg/kg with maximum volume 12 ml. The changes of hemodynamic parameters were recorded intraoperatively. The FLACC pain score, sedation score, duration of analgesia and requirement of analgesic were recorded in the recovery room.

Results: The demographic characteristic were comparable in both the groups. The mean duration of analgesia was significantly prolonged (707.3 ± 59.56 minutes) in group B compared to (411.83 ± 14.82 minutes) in group A. The requirement of first rescue analgesic medication was significantly prolonged in group B compared to group A ($P < 0.05$). Total analgesic consumption was significantly higher in group A (180 ± 70 mg) compared to group B (90 ± 70 mg) ($P < 0.05$)

Conclusion: Addition of clonidine 1µg/kg to ropivacaine 0.2 % in caudal analgesia significantly increases the duration of postoperative analgesia compared to plain ropivacaine 0.2% without any significant sedation.

Keywords: *clonidine, caudal analgesia, children, infraumbilical surgeries, ropivacaine.*

Cite This Article: Dr. Solanki, N.M., Dr. Rathod, A., Dr. Maheshwari, K., Dr. Bhimani, M. 2018. EFFECT OF CLONIDINE ADDED TO CAUDAL ROPIVACAINE IN PEDIATRIC INFRAUMBILICAL SURGERIES. *Bali Journal of Anesthesiology* 2(3): 65-71. DOI:10.15562/bjoa.v2i3.84

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INTRODUCTION

Caudal epidural block is a safe, reliable and easy method to administer and is therefore well-accepted technique for postoperative analgesia in lower abdominal surgeries especially in young children. There was a short duration of analgesia even with the use of long-acting local anesthetics like bupivacaine and ropivacaine.[1] The addition of adjuvants are required to prolong the duration of analgesia provided by a single caudal injection.

Ropivacaine, an amide local anesthetic has been used for caudal analgesia in children.[2] Ropivacaine has less cardiac and neurological toxicity than bupivacaine. When compared to bupivacaine, ropivacaine can allow early mobilization after surgery due to less motor effect and prolong the sensory effect.[3] The use of opioids and ketamine as an adjuvant with local anesthetic in caudal block was more common in British pediatric anesthetist (58%) as a survey done by Sanders JC in 2009.[4] Clonidine, an alpha-2 adrenergic agonist, produces analgesia without significant respiratory depression.[5]

We planned a prospective, randomized, double-blind study in our institute to compare the effects of clonidine with ropivacaine and ropivacaine alone through the caudal epidural block in children undergoing infraumbilical surgeries under general anesthesia.

DESIGN AND METHODS

The written and informed consent was taken from parents after explaining them in detail about the anesthetic procedure. This study was conducted in the pediatric surgical operation theater in our institute. A total 60 patients of American Society of Anesthesiologist physical status I-II of either sex, aged 1 to 12 years, weighing 5 to 30 kg, scheduled for elective infraumbilical surgeries were included for study. Exclusion criteria consisted of bleeding or coagulation test abnormalities, infection at the site of the caudal block, bony abnormality of the spine, neuromuscular disorders or hypersensitivity of any local anesthetic. The patients were assigned into two equal groups in a double-blinded by using computer-generated randomization numbers: Control group (Group A) ropivacaine 0.2% (1ml/kg) with maximum volume 12 ml and clonidine group (Group B) ropivacaine 0.2% (1ml/kg) with clonidine 1µg/kg with maximum volume 12 ml. The Anesthesiologist

who was performing the caudal block was blinded about the drug preparation and patients.

After shifting the patient into the operation room, multichannel monitor attached which included Electrocardiogram (ECG), Non-invasive measurement of Blood Pressure (NIBP), (O_2 Saturation (SpO_2), and End-Tidal CO_2 ($EtCO_2$). A good peripheral intravenous line was taken and injection glycopyrrolate 0.004mg/kg and injection ondansetron 0.15mg/kg were given. Intravenous induction was done with thiopental sodium 5-6mg/kg or inhalational induction of anesthesia was done with increasing concentration of sevoflurane (1-6%) with 50% nitrous oxide in oxygen. The caudal block was performed by using a 22-gauge hypodermic needle under complete aseptic precaution in left lateral position. The epidural space was localized and confirmed by loss of resistance to saline technique with a 2ml-syringe, and the appropriate drug injected into the caudal space slowly as per the group with continuous ECG monitoring. After placing a caudal block, the patient was turned supine. Intravenous succinylcholine 1-2 mg/kg was given to facilitate insertion of a supraglottic airway device or endotracheal tube. No analgesic was supplemented during the intraoperative period. The maintenance of anesthesia was done with assisted ventilation using sevoflurane (2-0.6%) or controlled ventilation using atracurium IV (0.5 mg/kg) with 50% nitrous oxide in oxygen. The surgical incision was made 5 minutes after caudal placement of drug. Whenever there is an increase in heart rate or systolic blood pressure within 15-20 minutes after the surgical incision was considered a failure of caudal analgesia. Intravenous fluid in the form of glucose/saline solution was infused as per requirement.

The intra-operatively concentration of sevoflurane, heart rate, NIBP, SpO_2, $EtCO_2$, and temperature were recorded every 10 minutes until the end of surgery. At the end of surgery, all the anesthetics gases were turned off and the residual neuromuscular block was antagonized with injection glycopyrrolate 0.008mg/kg and injection neostigmine 0.05mg/kg intravenously. The patients were extubated in a fully conscious condition and during inspiration. Duration of surgery, duration of anesthesia and postoperative complications like respiratory depression, nausea, vomiting and urinary retention were recorded.

In the recovery room hemodynamic parameter, sedation and pain score were recorded at a 10 min interval after extubation and thereafter at an interval of 1,2,4,6,8,10,12,15,18,21 and 24 hours. A four-point sedation score was employed to assess the postoperative sedation (0-spontaneous eye opening, 1-eye open on speech, 2-eye open on shake, 3-unarousable). Postoperative pain and duration of analgesia were evaluated by using the FLACC score (F= Face, L=Leg A= Activity, C= Cry, C=Consolability). The score 0 - no pain, 1 to 3 - mild pain, 4 to 7- moderate pain, 8 to 10 - severe pain and has a maximum score of 10.

The duration of analgesia was considered the time from caudal placement of the drug to the first recording of the FLACC pain score >4. Intravenous paracetamol 15mg/kg was administered as a rescue analgesia whenever pain score >4. The total doses of the paracetamol were recorded within 24 hours. A senior resident of the anesthesia department had observed the patients for the next 24 hours. The discharge of the patients had done on the next day. None of the patients complained of any side effects or untoward incident when they had come during the follow-up period.

The sample size represented by using formula $n= 4pq/E^2$ which is based on Hardy-Weinbergg principle. In this formula, p is the prevalence of infra-umbilical pediatric surgery at the civil hospital. The data were collected, tabulated and analyzed by using Microsoft Office Excel 2010 and Graph Pad Prism 6.05 (quickcalc) Software (GraphPad Software Inc., La Jolla CA, USA). Collected data were presented as mean ± SD and numbers as appropriate. Analysis of categorical data was done by using chi-square with Yate's correction and Fisher's exact test whichever appropriate. Analysis of continuous data was done by using an unpaired student's *t*-test. For all statistical analysis, a P-value of less than 0.05 was considered significant.

RESULTS

The demographic data such as age, sex, weight, ASA grade and device used to secure an airway were comparable in both groups. The two groups were comparable with regarding the duration of surgery, time to extubation from cessation of anesthesia ($P> 0.05$) and SpO_2 (>96%). (Table 1). Table 2 shows that the difference was found insignificant between two groups regarding the types of surgery.

Primary Outcome

Mean hourly pain score in the recovery room in both the groups were similar up to 4 hours after injection. Thereafter, the mean score in group A at 4,6,8, and 10 hours was significantly higher when compared to group B ($P <0.05$) (Figure 1). None of the children in both the groups had motor impairment on immediate postoperative period and during the next 24 hours period.

During the first 30 minutes in recovery room sedation score was above 1 in group B while in group A, sedation score was below 1. Thereafter,

Table 1 Demographic data in both groups

Patient characteristics	Group A (N=30)	Group B (N=30)	P Values
Age (years)	3.00 ± 1.58	3.24 ± 1.61	0.5623
Weight (kg)	11.07 ± 0.65	11.00 ± 0.53	0.6493
Sex (M:F)	29:1	29:1	1.000
ASA Grade I/II	26/4	27/3	1.000
Duration of Surgery(hr.)	1.32±0.65	1.28±0.67	0.8153
I-gel/ ET Tube Insertion	18/12	19/11	1.000
Time to extubation (Min)	4.32±1.65	4.58±1.76	0.5573
Postoperative SpO_2	97±2.56	96±2.86	0.1590

*ASA-American Society of Anesthesiologist
Data presented as mean ± SD or Number: *P-value < 0.05 is considered significant

Table 2 Types of Surgery

Surgical procedure	Group A (N=30)	Group B (N=30)	P Value
Inguinal hernia	5	7	0.7480
Hypospadias	20	16	0.4296
Orchidopexy	2	4	0.6707
Cystolithotomy	3	3	1.0000

Data presented as Number: *P-value < 0.05 is considered significant

Table 3 Comparison of pulse rate per minute in both groups

Duration (Time)	Group A (N=30)	Group B (N=30)	P Values
Basal	128.3 ± 14.22	127.1.7 ± 9.50	0.7187
5 min after caudal	134.7± 11.60	130.1 ± 9.50	0.0983
10 min	123.9± 11.63	112.3 ± 9.05	<0.0001*
20 min	120.2± 11.47	104.4 ± 9.82	<0.0001*
30 min	118.5± 11.87	91.4 ± 10.36	<0.0001*
40 min	112.97 ± 13.26	94.25 ± 7.87	<0.0001*
50 min	113.3 ± 12.69	99.5 ± 9.65	<0.0001*
60 min	112.3 ± 8.92	103.3 ± 11.94	0.0016*
70 min	113.4 ± 10.06	100.5 ± 10.51	<0.0001*
80 min	114.6 ± 8.70	102.2 ± 12.00	<0.0001*
90 min	128±28.23	103.6±7.97	<0.0001*

Data presented as mean ± SD or Number: *P value < 0.05 is considered significant

sedation score in both the groups was similar during 24 hours (Figure 2). There was no statistically significant difference in sedation score of patients in group B when compared to group A after 30 minutes of postoperative period (P >0.05).

Secondary Outcome

Table 3 shows that the baseline heart rate recorded before the induction of general anesthesia was the same in both the groups. The mean heart rate was lower in group B at a different time period as compared to group A (P < 0.05). None of the children in either group had a drop in heart rate to < 80beats/min.

There was no statistically significant difference between the two groups regarding the systolic blood pressure and post-operative complications such as vomiting, urinary retention and respiratory depression (P >0.05). (Table 4 and 5)

There was a prolonged duration of analgesia for 707.3 ± 59.56 minutes in group B as compared to 411.83 ± 14.82 minutes in group A. The requirement of rescue analgesic was less in group B as compared to group A (P < 0.05). Total analgesic consumption

Table 4 Comparison of Systolic blood pressure (mm of Hg) in both groups

Time	Group A (N=30)	Group B (N=30)	P Values
Basal	107.03±3.27	105.03±5.94	0.1116
5 min after caudal	105.05±4.37	103.07±6.04	0.1511
10 min	94.37±7.14	92.4±4.19	0.1976
20 min	91.07±6.90	89.1±5.03	0.2114
30 min	90.37±7.80	88.4±5.39	0.2598
40 min	91.03±11.63	88.43±6.21	0.2845
50 min	92.9±12.14	88.73±7.49	0.1148
60 min	93.33±11.97	90.6±8.36	0.3100
70 min	97.1±9.44	94.37±7.55	0.2211
80 min	97.73±7.95	94.33±8.43	0.1135
90 min	98.13±8.95	95.63±8.69	0.2769

Data presented as mean ± SD or Number: *P-value <0.05 is considered significant

Table 5 Postoperative complications

Sr. No.	Complications	Group A	Group B	P value
1	Vomiting	1	2	1.0000
2	Urinary retention	0	0	1.0000
3	Respiratory depression	0	0	1.0000
4	Miscellaneous	0	0	1.0000

Data presented as Number: *P-value < 0.05 is considered significant

Table 6 Drug Characteristics in both groups

Characteristics	Group A	Group B	P Value
Mean duration of analgesia(minutes)	411.83 ± 14.82	707.3 ± 59.56	<0.0001*
Total analgesic dose (mg)	180 ± 70	90 ± 70	<0.0001*

Data presented as mean ± SD or Number: *P-value <0.05 is considered significant

was statistically higher in group A (180 ± 70 mg) as compared to group B (90 ± 70 mg) (P < 0.05) (Table 6).

During the postoperative period, the requirement of paracetamol administration was once in seventeen patients and twice in 1 patient in group B as compared to once in twenty-two patients and twice in seven patients in group A (P <0.05). While twelve patients in group B and 1 patient in group A did not require additional paracetamol during the first 24 h study period, which was statistically significant (P <0.05).

DISCUSSION

Postoperative analgesia provides not only pain relief but also inhibits trauma induced nociceptive impulses to blunt autonomic reflexes.

Enteral and parenteral analgesics (both opioids and non-opioids), used for providing postoperative analgesia, are associated with risks like gastrointestinal bleeding, nausea, and vomiting, sedation, respiratory depression, hepatotoxicity, nephrotoxicity etc. The regional techniques including the caudal block, avoid most of the problems and it is possible to achieve analgesia with the minimum of drug dose and complications.[6]

The caudal epidural block is a popular regional anesthetic technique to provide postoperative analgesia in children undergoing lower abdominal surgeries as it is easy to perform and safe.

The major drawback of the caudal block is the short duration of analgesia with single shot local anesthetics injection. So several agents were tried as an adjuvant to local anesthetic to prolong the duration of analgesia with minimal side effects. [7]

Various additive agents like ketamine, clonidine, dexmedetomidine, tramadol, dexamethasone or neostigmine have been used as an adjuvant to local anesthetics to increase the duration of analgesia for the caudal blockade. But opioids have some adverse effect like nausea, vomiting, pruritus and the risk

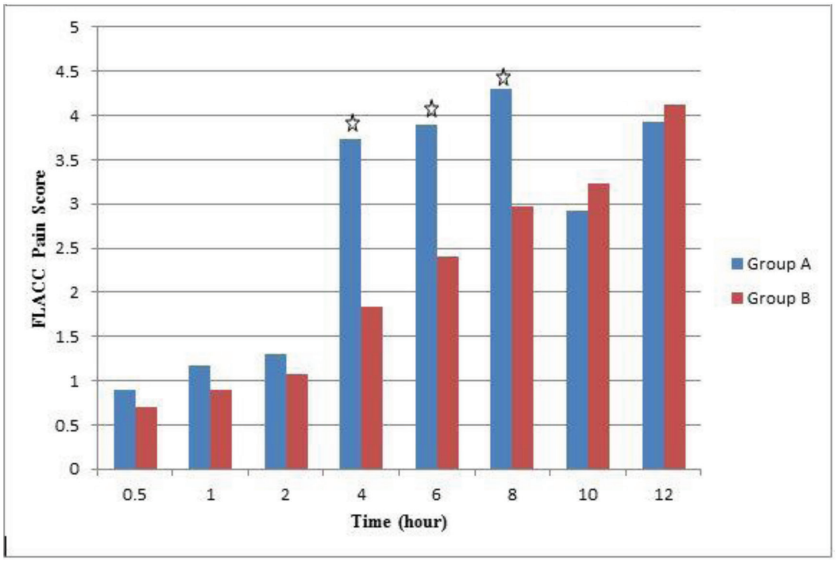

Figure 1 Post-operative pain score (FLACC Score) during the first 24 hours in both groups. The difference was statistically significant at 4, 6, and 8 hours after surgery. (Shows P-value < 0.05). Data presented as mean

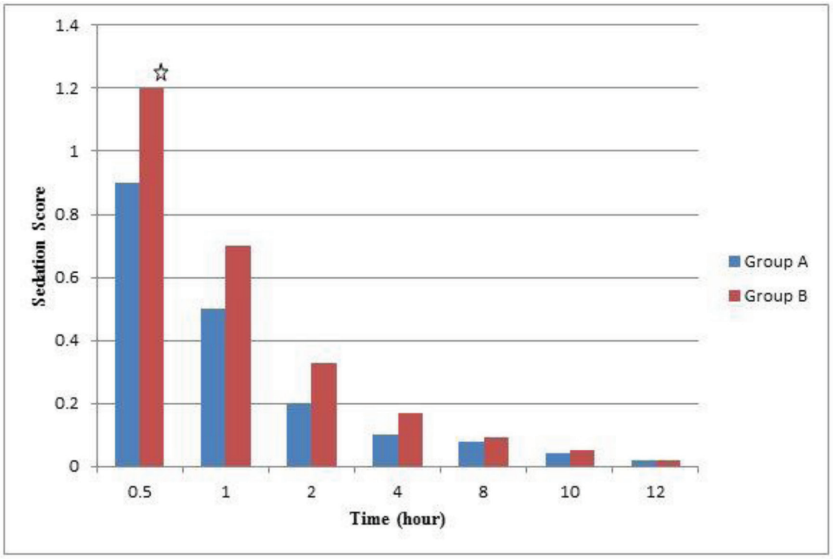

Figure 2 Post-operative sedation score (four-point sedation score) during the first 24 hours in both groups. Group B had sedation score above 1 in the immediate postoperative period as compared to Group A. (shows P-value <0.05). Data presented as mean

of respiratory depression. So the use of opioid has limited as an additive in children for caudal analgesia.[8] Recently ropivacaine is more commonly used the local anesthetic drug in caudal analgesia than bupivacaine due to lesser motor blockade and less cardiotoxicity.[3, 9,10]

Clonidine is an alpha-2 adrenoceptor agonist, used for treating hypertension previously in 70's and 80's, and presently it has been increasingly used for sedation, premedication, and as an adjuvant to caudal analgesia to prolong the duration of analgesia without significant respiratory depression.[11]

Epidural clonidine increases the duration of analgesia may be due to direct suppression of the spinal cord nociceptive neurons and also suppressing neurotransmission in peripheral sensory A, Delta, and C nerve fibers or crossing of blood-brain barrier and interaction with alpha-2 adrenoceptors at spinal and supraspinal sites.

Nishina K *et al.*[12] noted that clonidine may induce vasoconstriction through alpha-2b adrenoceptors located at the peripheral vascular smooth muscles.

Negri PD *et al.*[13] demonstrates that S ketamine-ropivacaine mixture provides better postoperative analgesia than clonidine-ropivacaine mixture without any significant adverse effect.

Gupta S *et al.*[14] reported that the addition of dexmedetomidine 2μg/kg to caudal ropivacaine 0.2% significantly prolonged postoperative analgesia than clonidine 2μg/kg without any side effects.

Kaul A *et al.*[15] reported that caudal clonidine-bupivacaine mixture is a safe alternative to bupivacaine alone for prolonging postoperative analgesia in pediatric day care surgeries.

Several studies reported that 1-2μg/kg clonidine with 0.25% bupivacaine prolonged the duration of caudal analgesia ranged from 9.8 hours to 16.4 hours.[16-17]

Bajwa *et al*[18] found that 0.25% ropivacaine with 2μg/kg clonidine prolonged the mean duration of analgesia 13.4 hours and 8.5 hours with 0.25 % plain ropivacaine.

We found that caudal 0.2% ropivacaine alone provided analgesia for 411.83 ± 14.82 minutes while 0.2% ropivacaine with 2μg/kg clonidine prolonged analgesia significantly up to 707.3 ± 59.56 minutes.

Luz *et al.*[19] found that using 0.1% ropivacaine in caudal anesthesia had a shorter duration of analgesia when compared to 0.2% ropivacaine and 0.2% bupivacaine.

Ivani G *et al.*[20] stated that lower concentration of caudal ropivacaine produces a lesser postoperative motor blockade and adequate sensory block as compared to caudal bupivacaine.

Balasubramanian S *et al.*[21] reported that combination of 1μg/kg clonidine with 0.1% ropivacaine significantly increased the duration of analgesia as compared to plain ropivacaine while Laha A *et al.*[22] found that 2μg/kg clonidine with 0.2% ropivacaine increases the duration of analgesia with lesser motor blockade and without any adverse effects.

Clonidine causes dose-dependent postoperative sedation in children. Some studies reported that caudal ropivacaine-clonidine does not produce significant sedation postoperatively in children.[18,23]

In our study, there was no significant difference in sedation score in both the groups after 30 minutes of the post-operative period.

The major side effects of epidural clonidine are hypotension and bradycardia. Epidural administration of clonidine caused bradycardia due to high vagal tone from central stimulation of parasympathetic nervous system as well as reduced sympathetic drive.[24]

We found that there was a statistically significant decrease in the heart rate, 10 minutes after caudal block in group B as compared to group A (P value of <0.05). However, none of the children required drug intervention for a decrease in the heart rate as it was not below the defined criteria.

The stimulation of alpha-2 inhibitory neurons in the medullary vasomotor center of the brainstem causes hypotension with epidural clonidine.[25] We did not observe any significant fall in the systolic blood pressure in both the groups.

Ali Ghulam *et al.*[26] concluded that a combination of clonidine with ropivacaine prolonged the duration of caudal analgesia and decreased the requirement of rescue analgesia compared to ropivacaine alone without postoperative sedation.

We found a similar result with the addition of 1μg/kg clonidine to 0.2 % ropivacaine in caudal analgesia.

Habre W *et al.*[27] found that 0.25% caudal ropivacaine (1ml/kg) produces a maximal plasma concentration of 0.72±0.24mg/L, while Knudsen K *et al.*[28] reported that intravenous infusion of ropivacaine produces the maximally tolerated plasma concentration in adult volunteers (2.2±0.8mg/L).

Therefore, in our study 0.2% 1ml/kg ropivacaine has been chosen and none of the children in both the groups found apparent motor deficit.

CONCLUSION

Caudal ropivacaine-clonidine increases the duration of postoperative analgesia compared to ropivacaine alone without any significant adverse effects in children undergoing infraumbilical surgeries.

REFERENCES

1. Verghese ST, Hannallah RS. Postoperative pain management in children. Anesthesia Clin North America. 2005; 23: 163–84. DOI: 10.1016/j.atc.2004.11.008
2. McClure JH. Ropivacaine. Br J Anesth. 1996; 76: 300–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8777115
3. Brockway MS, Bannister J, McClure JH, et al. Comparison of Extradural Ropivacaine and Bupivacaine. Br J Anesth. 1991; 66: 31-7. DOI: 10.1093/bja/66.1.31
4. Sanders JC. Pediatric regional anesthesia, a survey of practice in the United Kingdom. Br J Anesth. 2002; 89: 707-10. DOI: 10.1093/bja/89.5.707
5. Cook B, Dayle E. The use of additives to local anesthetic solutions for caudal epidural blockade. Pediatric Anesth. 1996; 6: 353–9. DOI: 10.1046/j.1460-9592.1996.d01-3.x
6. Gehdoo RP. Postoperative pain management in pediatric patients. Indian J Anaesth. 2004;48(5): 406-14. Available from: https://www.medind.nic.in>iad
7. Shukla U, Prabhakar BT, Malhotra K. Postoperative analgesia in children when using Clonidine or fentanyl with Ropivacaine given caudally. J Anaesthesiol Clin Pharamacol. 2011; 27: 205-10. DOI: 10.4103/0970-9185.81842
8. Ansermino M, Basu R, Carolyne M. Nonopioid additives to local anesthetics for caudal blockage in children: A review article. Paediatr Anaesthe. 2003; 13: 561-73. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12950855
9. Yildiz TS, Korkmaz F, Solak M, et al. Clonidine addition prolongs the duration of caudal analgesia. Acta Anesthesiol Scand. 2006; 50: 501-4. DOI: 10.1111/j.1399-6576.2005.00941.x
10. Tripi PA, Palmer JS, Thomas S, et al. Clonidine increases duration of Bupivacaine caudal analgesia for ureteroneocystostomy: A double-blind prospective 1 trial. J Urol. 2005; 174: 1081-3. DOI: 10.1097/01.ju-0000169138. 90628.b9
11. Lonnqvist PA. Adjuncts to caudal block in children-Quovadis? Br J Anesth. 2005; 95: 431-3. DOI: 10.1093/bja/aei221
12. Nishina K, Mikawa K, Shiga M, et al. Clonidine in pediatric anesthesia. Pediatric Anesth. 1999; 9: 187-202. DOI: 10.1046/ j.1460-9592.1999.00379.x
13. Negri PD, Ivani G, Visconti C, et al. How to prolong postoperative analgesia after caudal anesthesia with Ropivacaine in children: S-ketamine versus Clonidine. Pediatric Anesth. 2001; 16: 679-83. Available from: https://doi.org/10.1046/j.1460-9592.2001.00742.x
14. Gupta S, Pratap V. Addition of Clonidine or dexmedetomidine to Ropivacaine prolongs caudal analgesia in children. Indian J of pain. 2014; 28: 36-41. DOI: 10.4103/0970-5333.128892
15. Kaul A, Pant D, Sood J. Caudal Clonidine in daycare pediatric surgery. Indian J of Anesth. 2009; 53: 450-4. Available from: http://www.ijaweb.org/text.asp?2009/53/4/450/60316
16. Jamali S, Monin S, Begon C, et al. Clonidine in pediatric caudal anesthesia. Anesth Analg. 1994; 78: 663-6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8135384
17. Lee JJ, Rubin AP. Comparison of a Bupivacaine Clonidine mixture with plain Bupivacaine for caudal analgesia in children. Br J Anesth. 1994; 72: 258-62. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8130041
18. Bajwa SJ, Karun J, Bajwa SK, et al.Caudal Ropivacaine-Clonidine: A better post-operative analgesic approach. Indian J Anesth. 2010; 54: 226-30. DOI: 10.4103/0019-5049.65368
19. Luz G, Innerhofer P, Häussler B, et al. Comparison of Ropivacaine 0.1% and 0.2% with Bupivacaine 0.2% for single-shot caudal anesthesia in children. Pediatric Anesth. 2000; 10: 499-504. DOI: 10.1046/ j.1460-9592.2000.00532.x
20. Ivani G, Mereto N, Lampugnani E, et al. Ropivacaine in pediatric surgery: Preliminary results. Pediatric Anesth 1998; 8:127-9. Available from: https://doi.org/10.1046/j.1460-9592.1998.00246.x
21. Balasubramanian S, Sanmugapiriya K, Sureshkumar K, et al. Comparison of Ropivacaine and Ropivacaine with Clonidine for caudal analgesia in pediatric patients for lower abdominal surgeries. Int J Sci Stud. 2016; 3: 1-5. DOI: 10.17354/ijss/2016/01
22. Laha A, Ghosh S, Das H. Comparison of caudal analgesia between Ropivacaine and Ropivacaine with Clonidine in children: A randomized controlled trial. Saudi Journal of Anesthesia. 2012; 6: 197-200. DOI: 10.4103/1658-354X.101199
23. Manikram A, Vakamudi M, Parmeswari A, et al. Efficacy of Clonidine as an adjuvant to Ropivacaine for caudal analgesia in children undergoing subumbilical surgery. J of Anesth Clin Phar. 2012; 28: 185-9. DOI: 10.4103/0970-9185.94839
24. Aantaa R, Scheinin M. Alpha -2 adrenergic agents in anesthesia. Acta Anesthesiol Scand. 1993; 37: 433-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8395129

25. De Beer DA, Thomas ML. Caudal additives in children solutions or problems? Br J Anesth. 2003; 90: 487-98. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12644422
26. Ali G, Kala N, Rather MA, et al. Comparative evaluation of caudal Ropivacaine and Ropivacaine with Clonidine for postoperative analgesia in children. IOSR, JDMS. 2015; 14: 50-4. DOI: 10.9790/0853-14935054
27. Habre W, Bergesio R, Johnson C, et al. Pharmacokinetics of Ropivacaine following caudal analgesia in children. Pediatric Anesth. 2000; 10: 143–7. DOI: 10.1046/j.1460-9592.2000.00454.x
28. Knudsen K, Beckman Surkula M, et al. Central nervous and cardiovascular effects of i.v. infusions of Ropivacaine, Bupivacaine, and placebo in volunteers. Br J Anesth. 1997; 78: 507-14. DOI: 10.1093/bja/78.5.507