Original article

A Comparative Study of Post-Operative Pain Relief with Dexmedetomidine versus Clonidine as Adjuvants in 0.2% Ropivacine for Caudal Epidural Block in Children Undergoing Lower Abdominal Surgeries

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Abstract:

Context: Acute postoperative pain relief is accepted as an integral part of paediatric anesthetic practice. A difficulty in distinguishing pain from hunger or fear in pre-verbal children and the notion that children do not respond to pain in the same way as adults do, combined with an excessive fear of respiratory depression caused by opioids had lead to pain being under treated in children. Recent evidence suggests that pain causes psychological and physiological abnormalities in children similar to that of adults and therefore must be addressed. We designed a prospective, randomized, study to compare the efficacy and safety of caudal ropivacaine with additive dexmedetomidine versus clonidine in providing postoperative analgesia in children undergoing lower abdominal surgeries. We also studied the haemodynamic and respiratory changes in both groups and looked for any complications.

Methods: A comparative prospective study was carried out amongst 100 ASA status I or II male patients, in the age group 2 to 8 years undergoing lower abdominal surgeries. The study was carried out from Jan. 2012 to Dec. 2013. Patients were divided into two groups and were given caudal epidural analgesia with the drugs as given below after administering general anaesthesia to them:

Group A**:** 0.2% Inj Ropivacaine+ Inj. Clonidine 1mcg/kg making the volume 1ml/kg

Group B**:** 0.2% Inj. Ropivacaine + Inj. Dexmedetomidine 1mcg/kg making the volume 1ml/kg

Patients were monitored intraoperatively for Heart Rate (HR), Non Invasive Mean arterial Pressure (MAP), SpO_2, ECG and end tidal carbon dioxide at induction, after intubation and then after caudal block and every 10 min then on till end of surgery. Post operatively sedation scores and VAS score for pain relief were recorded.

Results: SPSS release 12.0.1 was used for statistical analysis. Numerical Variables were presented as mean and standard deviation (SD). To estimate differences in normally distributed continuous outcome variables, student's unpaired t- test was used and p- value of <0.05 was considered statistically significant. The heart rate showed an increase at intubation and started showing a decline after caudal. The MAP showed an increase at intubation and fell after caudal. The fall in HR and MAP from baseline to minimum was significant but required no intervention. Though there was no significant difference in postoperative sedation among the two groups but all the patients were calm and awake or sleeping and aroused easily. There was a significant increase in the duration of analgesia as measured by VAS in Group B.

Conclusion: We conclude that when given as a caudal additive to 0.2% ropivacaine, dexmedetomidine 1 mcg/kg provided significantly longer postoperative analgesia, and good hemodynamic stability, without producing excessive sedation or any major side effects when compared to clonidine 1mcgs/kg

Key words: Analgesia; Pain Measurement; Clonidine; Dexmedetomidine; Anesthesia, Caudal

Introduction:

Management of perioperative pain is the cornerstone of a good and well-balanced anaesthesia technique. Postoperative pain especially if it is poorly controlled can result in harmful acute effects like adverse physiological responses and chronic effects like delayed long term recovery and development of chronic pain.[1]

This is even more important when the patient is a child. Acute postoperative pain relief has now been accepted as an integral part of paediatric anesthetic practice. Even then, postoperative pain relief in children is often inadequate. The problem of communication with children, especially the sick ones make pain assessment difficult. A difficulty in distinguishing pain from hunger or fear in pre-verbal children and the notion that children do not respond to pain in the same way as adults do, combined with an excessive fear of respiratory depression caused by opioids lead to pain being under treated in children, in the past.[2]

Recent evidences suggest that pain causes psychological and physiological abnormalities in children similar to that of adults. Paediatric regional anaesthesia is commonly used with general anaesthesia (GA) and is a component in the multimodal approach to pain management in pediatric patients and provides excellent postoperative analgesia. Caudal epidural analgesia is one of the most popular, commonly practiced, safe and reliable regional blocks in paediatric anaesthesia with a predictable level of blockade.[3]

It provides intra and post-operative analgesia in patients undergoing lower abdominal, urological and lower limb surgeries. Gradual offset usually provides analgesia beyond the duration of surgery, with a smooth recovery period and good postoperative pain control.[4] This benefit is especially important in ambulatory and day care surgery patients because it reduces analgesic requirements and facilitates early discharge. However, the efficacy of this technique in providing good postoperative analgesia does depend on the duration of action of the local anesthetic used.

Ropivacaine, a long acting local anaesthetic, via caudal route is well entrenched in pediatric anaesthesia practice.[5] However its main disadvantage is a short duration of action after a single shot injection. The use of an indwelling caudal catheter raises the risk of infection and catheter migration. Prolongation of caudal block using a single shot technique can however be achieved by addition of various adjuncts like epinephrine, ketamine and various opioids.[4]

Alpha 2 adrenergic agonists are the latest in the list of caudal additives. Clonidine, an Alpha 2 adrenergic agonist, when given epidurally can prolong sensory block to a much greater extent than motor block. This seems to be mediated by opening of Potassium channels and subsequent hyperpolarization rather than its Alpha 2 agonist effect[6]. It also decreases the immune stress and the cytokine response to pain.[7] However epidural clonidine can produce bradycardia, hypotension, dry mouth and sedation.[8]

Dexmedetomidine is the newer centrally acting Alpha 2 selective agonist. It is 10 folds more alpha selective than clonidine.[9] Studies in adults have shown epidural dexmedetomidine also reduces intraoperative anaesthetic requirements, improves

postoperative analgesia and prolongs both sensory and motor block.[10]

We designed a prospective, randomized study to compare the efficacy and safety of caudal ropivacaine with dexmedetomidine versus clonidine in providing postoperative analgesia in children undergoing lower abdominal surgeries. We also studied the haemodynamic and respiratory changes in both groups and looked for any complications.

Materials and Methods:

A comparative study was carried out after obtaining informed parental consent and Ethics Committee approval. A total of 100 ASA status I or II male patients, in the age group 2 to 8 years undergoing lower abdominal surgeries were prospectively enrolled in this study. The study was carried out for two years from January 2012 to December 2013. A pilot study done in our institute showed that the minimum sample size needed for the study to be statistically significant was 25; therefore we took 50 in each group.

Study exclusion criterion included a history of a known allergy to any of the study group drugs, a known or suspected coagulopathy, any infection at the site for caudal block or a history of developmental delay or mental retardation which could make pain assessment difficult or unreliable.

Using a computer-generated list, the subjects were assigned randomly into two groups: Group A and Group B.

Group A: patient received 0.2% Inj Ropivacaine+ Inj. Clonidine 1mcg/kg making the volume 1ml/kg

Group B: patient received 0.2% Inj. Ropivacaine + Inj. Dexmedetomidine 1 mcg/kg making the volume 1 ml/kg

All personnel providing direct patient care were blinded to the caudal medication administered. All the drugs were prepared by a designated senior resident of the department based on the subject's weight and the randomization chart and they were just labeled with the patient's identity number.

Baseline physical examination including age, weight, airway, pulse, vital parameters and systemic examination was done for all patients and recorded. Baseline investigations like hemogram and urine analysis were done for all. The study procedure including the Pain and Sedation scores that were to be used post operatively was explained to the patient's guardian. In our hospital all paediatric cases are admitted a night prior to surgery and an intravenous (IV) access with 22/24 G cannula is secured by the ward staff.

On arrival to the operation theatre, patients' nil oral status was confirmed. IV premedication was given with inj glycopyrrolate 5mcg/kg and midazolam 0.05 mg/kg as per department protocol. Maintenance fluid Isolyte P/Ringer Lactate at the rate of 4ml/kg was started. All patients were induced intravenously with inj Propofol 1%, 2mg/kg till eyelash reflex was lost. After confirming adequate mask ventilation, Inj Vecuronium bromide 0.1 mg/kg was given. Laryngoscopy and intubation with adequate size endotracheal tube was done to secure the airway.

After securing the airway, the patient was made lateral for the caudal block. An assistant maintained position. Patient received caudal block with 22G hypodermic needle and drug was injected as per the group to which the patient was allotted. The lead investigator of the study gave all blocks. Patient was immediately turned supine after caudal. Anaesthesia was maintained with Oxygen: Air (50:50), sevoflurane and intermittent boluses of Inj. Vecuronium. No other narcotics, analgesics, sedatives or anti emetics were administered intraoperatively as per protocol. If however patient showed an increase in HR and MAP more than 30% at incision, it was taken as failure of caudal block and analgesia was supplemented with

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2mcg/kg Inj Fentanyl. At the end of surgery, patient was reversed with Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 8 mcg/kg IV and extubated awake and shifted to the PACU.

Intra operative Monitoring - Heart Rate (HR), Non Invasive Mean arterial Pressure (MAP), SpO_2, ECG and end tidal carbon di oxide ($ETCO_2$) were monitored and noted before induction, after intubation and then after caudal block and every 10 min then on till end of surgery.An intra- and post operative fall of HR and MAPof more than 30% from the baseline values was considered as bradycardia or hypotension respectively and were treated with rapid infusion of fluids or if that failed, with Inj Atropine 0.01mg/kg or Inj Ephedrine in aliquots of 0.02mg/kg as appropriate

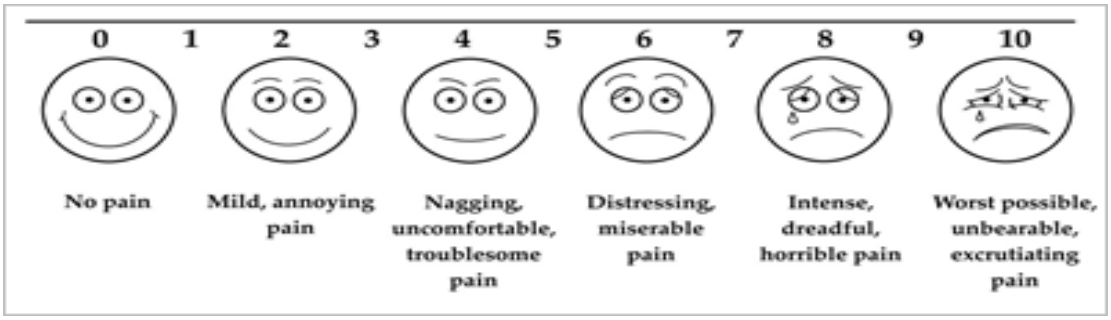
Post operative Monitoring - Post operatively in the ward, HR, MAP, respiratory rate (RR) and SPO_2 were recorded initially every 10 minutes for half an hour and thereafter, at intervals of 1, 2, 4, 6, 8, 12, 18 and 24 hours from Extubation. Simultaneously pain score and Sedation score were also noted. Respiratory depression was defined as decrease in post operative SpO2 to less than 93% or post-operative RR less than 12/min. This was then treated with supplemental oxygen via Hudson's mask.

Sedation was monitored using **5 Point Sedation Score [PSS]** as follows:

1- Alert and wide awake
2- Arousable to verbal command
3- Arousable with gentle tactile stimulation
4- Arousable with vigorous shaking
5- Not arousable

Post operative pain - As all our patients were 2 years and older the Visual Analogue Scale (VAS) was used for post op pain and adequacy of analgesia.

VAS



For patients showing a VAS score of more than 3, rescue analgesia was given with inj paracetamol 5 mg/kg and this was recorded. Duration of analgesia was defined as time between caudal drug injection and rescue analgesic administration. Administration of rescue analgesia was considered as end point of the study for that particular case. Any other complications like nausea, vomiting, and urinary retention were also noted and recorded. An anaesthesiologist who was blinded to both the drug used as well as the intraoperative course noted all postoperative recordings.

Statistical Analysis – SPSS version 12.0 was used for statistical analysis. Numerical Variables were presented as mean and standard deviation (SD). To estimate differences in normally distributed continuous outcome variables, student's unpaired t- test was used. As p- value of <0.05 was considered statistically significant.

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Results:

We had 3 cases of failed caudal requiring intervention in our study, one in Group-A and two in Group-B. All three were excluded from the study result calculations.

Table 1: Demographic data reported as mean and SD

Variable	Group	Number	Mean	SD	P value	Significance
Age (in Years)	A	49	4.87	1.82	0.24	Not Significant
	B	48	4.45	1.68		
Weight (in Kgs)	A	49	17.22	5.49	0.84	Not Significant
	B	48	17.42	4.01		
ASA Status (I or II)	A	49	36: 14	Not applicable		Comparable
	B	48	40: 10			
Duration of surgery (in min.)	A	49	113.10	22.32	0.15	Not Significant (NS)
	B	48	105.87	27.09		

The demographic data was comparable between Group A (Ropivacaine + Clonidine) and Group B (Ropivacaine + Dexmedetomidine).

Table 2: Intraoperative Heart Rate

	Group	Number	Mean (Per Min.)	SD	P-value	Significance
Baseline	A	49	107.04	12.56	0.21	NS
	B	48	104.11	10.01		
After intubation	A	49	124.44	13.61	0.49	NS
	B	48	122.66	11.35		
After caudal	A	49	119.00	15.48	0.46	NS
	B	48	121.16	13.30		
Lowest value intraop	A	49	90.12	6.52	0.26	NS
	B	48	91.71	7.21		
Time (in minutes) after caudal for lowest value	A	49	32.24	6.97	0.06	NS
	B	48	34.67	5.36		

The heart rate showed an increase at intubation and started showing a decline after caudal. Though the fall in HR from baseline to minimum was significant, however it was not greater than 30% in either group to mandate any intervention.

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Table 3: Trends in intraoperative Mean Atrial Pressure (MAP)

	Group	Number	Mean (mm Hg)	SD	P-value
Baseline	A	49	82.34	6.98	0.89
	B	48	82.52	6.87	
After intubation	A	49	86.84	4.89	0.88
	B	48	86.70	4.41	
After caudal	A	49	86.58	3.94	0.25
	B	48	85.66	3.91	
Lowest value intraop	A	49	75.26	12.06	0.18
	B	48	78.15	8.84	
Time (in minutes) after caudal for lowest value	A	49	40.82	3.76	0.18
	B	48	42.06	5.29	

The MAP showed an increase at intubation and fell after caudal. The fall in MAP from baseline to minimum was significant, however it was not greater than 30% in either group to mandate any intervention.

Table 4: Postoperative Respiratory Rate (RR)

	Group	Number	Mean	SD	P value
At 10 minutes	A	49	23.50	4.73	0.16 (NS)
	B	48	24.64	3.02	
Minimum RR postop	A	49	20.18	3.66	0.29 (NS)
	B	48	21.00	3.89	

There were no cases requiring any supplemental oxygen intervention in the postop period in our study.

Table 5: Postoperative Sedation Scores

Time	Group	Number	Mean	SD	P value	Significance
1 hour	A	49	2.12	0.57	0.15	Not Significant
	B	48	2.27	0.44		
2 hours	A	49	1.58	0.12	0.33	Not Significant
	B	48	1.62	0.26		
4 hours	A	49	1.52	0.09	0.39	Not Significant
	B	48	1.55	0.23		
6 hours	A	49	1.02	0.13	0.11	Not Significant
	B	48	1.06	0.11		
8 hours	A	49	1.03	0.02	0.05	Not Significant
	B	48	1.02	0.03		
12 hours	A	49	1	0	Not Significant	
	B	48	1	0		

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There was no significant difference in postoperative sedation noticed between the two groups. But all children in both groups were calm and awake or sleeping and aroused easily. Sedation was not monitored after 12 hours.

Table 6: Duration of analgesia (in hours)

	Number	Mean	SD	P value	Significance
Group A	49	9.56	0.85	<0.01	Extremely significant
Group B	48	14.21	1.33		

There is a significant increase in the duration of analgesia as measured by VAS in Group B.

Table 7: Complications

	Number	Nausea	Vomiting	Urinary Retention
Group A	49	2 (4.02%)	1 (2.04%)	0 (0.0%)
Group B	48	2 (4.08%)	2 (4.08%)	0 (0.0%)

The incidence of nausea and vomiting among the groups was minimal and not statistically significant. No urinary retention was seen in any patient. No other side effects were seen.

Discussion:

Caudal epidural analgesia is one of the most common and safe regional blocks in pediatric anaesthesia and it is recommended for most surgical procedures on the lower part of the body. Its popularity and effectiveness is only limited by the short duration of actions of the various local anaesthetics, which are used to give the block. The commonly used drug for caudal epidural is bupivacaine. Ropivacaine which was introduced in 1996 has a better safety profile when compared to bupivacaine because of lower cardio toxicity, a higher seizure threshold, greater motor-sensory differentiation and therefore lesser motor block.[11,12] However studies have shown that epidurally administered ropivacaine is 40% less potent than bupivacaine and has a shorter duration of action.[13-15] Therefore focus in recent times has been on finding the perfect additives to caudal ropivacaine which can prolong the duration of analgesia while maintaining the safety profile in children. Alpha 2 adrenoceptor agonists have been studied as additives to bupivacaine.[16] A few studies in recent times have also evaluated different doses of these additives with varying concentrations of ropivacaine.[17,18]

Our prospective, randomized, double blind study compared the efficacy and safety of additives clonidine and dexmedetomidine with caudal ropivacaine in providing postoperative analgesia in children undergoing lower abdominal surgeries. We also studied the hemodynamic and respiratory changes in the two groups and looked for complications if any. We enrolled 100 male children in the age group of 2-8 years in our study. As most cases were hydroceles, circumcisions, orchidopexy, hypospadias' repairs and hernias, we restricted our study to the male population to prevent under representation and gender bias in the results.

In 1999, Breschan [19] reported life threatening postoperative apnoea in a full term neonate undergoing inguinal herniorrhaphy and orchidopexy who received light inhalation anaesthesia combined with caudal block with 1 ml/kg ropivacaine 0.2% plus 2mcg/kg clonidine.

Another case report by Bouchut JC, Dubois R, Godard J [20] warns of the risk of postoperative apnoea in a preterm neonate who had clonidine 1.25 mcg/ kg added to the caudal injection for hernia repair. Clonidine may be therefore unsafe for use in neonates and preterm infants, and until further studies have evaluated the association of dose and side effects, its use in this group of patients cannot be recommended. Since the safety of clonidine in neonates is debatable, we selected patients in the age group 2-8 years for our study.

The Heart rate and the MAP showed an initial increase in both groups at intubation but steadily fell after the caudal was given (Tables 2 & 3). The minimum heart rate was recorded at 32.24±6.97 minutes in Group A and at 34.67±5.36 minutes in Group B, which were comparable. The minimum MAP was 75.26 ±12.06 mmHg in Group A at 40.82±3.76 minutes and 78.15±8.84 mmHg in Group B at 42.06±5.29 minutes. Though the fall in HR from baseline to minimum was significant, however it was not greater than 30% in either group to mandate any intervention. A similar observation was made by Gupta and Virender in their study comparing caudal clonidine 2 mcg/kg or dexmed 2 mcg/kg with 0.2% ropivacaine.[17] The maximum fall in their study occurred at 0-15 minutes in both groups, which can be explained probably by the higher doses of the Alpha 2 adrenoceptor agonists used in their study.

Both clonidine and dexmedetomidine when given by the neuraxial route decrease the electrical activity of preganglionic sympathetic nerves. Once systemically absorbed they also cause stimulation of Alpha 2 inhibitory neurons in the medullary vasomotor center (Nucleus Reticularis Lateralis) of the brainstem, which leads to a reduction in norepinephrine release and sympathetic nerve outflow from the CNS to the peripheral tissues. Both these contribute to the bradycardia and hypotension caused by epidural and dexmedetomidine.[21]

There was no difference in the postoperative sedation scores in the two groups (Table 5). However it was found that children were either calm and alert or sleepy and easily aroused. No child in either group was found to be distressed or fussy in the first 8 hours of the study. Gupta et al observed similar results in their study.[17] Anand et al who studied effects of dexmedetomidine added to caudal in paediatric lower abdominal surgeries concluded that dexmedetomidine provides an interesting quality of sedation that permits arousal with gentle stimulation.[22]

The analgesic actions of α-2adrenoceptor agonists are attributed to various factors. The activation of inwardly rectifying G1-protein-gated potassium channels results in membrane hyperpolarization decreasing the firing rate of excitable cells in the central nervous system (CNS) and contributes to the mechanism of inhibitory neuronal action of α-2adrenoceptor agonists.[23] Another prominent physiologic action of α2-adrenoceptors is their reduction of calcium conductance into the cell, thus inhibiting neurotransmitter release. Therefore α2-adrenoceptor agonists affect analgesia in two different ways, on one side the nerve is prevented from ever firing, and in the second, it cannot propagate its signal to its neighbor.[17] Administration of an α2-agonist via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation. This effect is due to the sparing of supraspinal CNS sites from excessive drug exposure, resulting in excellent analgesia without heavy sedation.[24]

Our study found that duration of post operative analgesia was significantly longer in the dexmedetomidine group (14.21±1.33 hours) in comparison to the clonidine group (9.56 ±0.85). Raval and Karthik in their study in 2014, compared

clonidine 1mcg/kg and dexmed 1 mcg /kg as additives with 0.25% bupivacaine for caudal in children and found that dexmed provided a longer duration of post op analgesia compared to clonidine (14.16±1.65 vs 11.24±2.48) [25] Gupta and Virender in their study comparing double the dose of clonidine and dexmed with ropivacaine also found that analgesia lasted longer in the dexmed group (17.6±2.9 vs 10.1±3.2). [17] Neogi et al compared the alpha 2 adrenoceptor agonists in the dose of 1mcg/kg but with 0.25% ropivacaine and found that dexmedetomidine provided far superior post operative analgesia.[18] Both the groups did not show any significant incidence of major side effects like pruritis, nausea, vomiting or urinary retention.

Conclusion:

We conclude that when given as a caudal additive to 0.2% ropivacaine, dexmedetomidine 1 mcgs/kg provided significantly longer post operative analgesia and good hemodynamic stability, without producing excessive sedation or any major side effects when compared to clonidine 1mcgs/kg.

References:

1. Hurley RW, Murphy JD, Wu CL. Acute postoperative Pain. In:Miller RD. Miller's Anesthesia: 8th ed. Philadelphia:Elsevier Saunders; 2015.p.29-74
2. Krane EJ. Delayed respiratory depression in a child after caudal Morphine , Anesth Analg 1988; 67:79-82.
3. Lonnqvist P A. Additives to caudal block in children. Br J Anaesth 2005;95:431-3.
4. Cook B, Dayle E. The use of additives to local anaesthetic solutions for caudal epidural blockade. Paediatric Anesthesia 1996; 6: 353-9.
5. Ivani G, Lampugnani E, Torre M, Calevo Maria G, DeNegri P, Borrometi F, Messeri A , Calamandrei M, Lonnqvist PA, Morton NS. Comparison of ropivacaine with bupivacaine for paediatric caudal block. Br J Anaesth. 1998;81(2):247-48.
6. Kroin JS, Buvannendran A, Beck DR et al: Clonidineprolongation of lignocaine after sciatic nerve block in rats is mediated via the hyperpolarization-activated cation current, not by alphaadrenoreceptors. Anaesthesiology. 2004;101(2):488-494.
7. Wu C-T, Jao S-W, Borel CO, et al: The effect of epidural clonidine on perioperative cytokine response, postoperative pain and bowel function in patients undergoing colorectal surgery. AnaesthAnalg. 2004; 99(2):502-509.
8. De Kock M: Site of hemodynamic effects of alpha2-adrenergic agonists , Anaesthesiology. 1991;75(4): 715-716
9. Kalso EA, Poyhia R, Rosenberg PH: Spinal antinociception by dexmedetomidine, a highly selectivealpha 2-adrenergic agonist. Pharmacol Toxicol.1991;68(2):140-143
10. Grewal A:Dexmedetomidine :New avenues. J AnaesthesiolClinPharmacol. 2011;27(3): 297-302.
11. Mc Clure JH: Ropivacaine. Br J Anaesth. 1996;76(2):300-07
12. Moller R, Covino BG: Cardiac electrophysiologic properties of bupivacaine andlidocaine compared with those of ropivacaine, a new amide local anaesthetic. Anaesthesiology. 1990;72(2):322-329
13. Polley LS, Columb MO, Naughton NN, et al: Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: implications for therapeutic indexes. Anaesthesiology.1999;90(4)944-95.
14. Capogna G, Celleno D, Fusco P, et al: Relative potencies of bupivacaine and ropivacaine for analgesia in labour. Br J Anaesth.1999;82(3)371-373.
15. Lacassie HJ, Columb MO, Lacassie HP, Lantadilla RA: The relative motor blocking potencies of epidural bupivacaine and ropivacaine in labour. Anaesth Analg. 2002;95(1):204-208
16. El-HennawyAM, Abd-Elwahab AM, Abd-Elmaksoud AM, El-Ozairy HS, Boulis SR. Addition of clonidine or

dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anaesth. 2009;103:268–74

17. Gupta S, Pratap V. Addition of Clonidine or Dexmedetomidine to Ropivacaine prolongs caudal analgesia in children. Indian J Pain 2014;28:36-41
18. Neogi M, Bhattacharjee DP, Dawn S, Chatterjee N. A comparative study between clonidine and dexmedetomidine used as adjuncts to ropivacaine for caudal analgesia in paediatric patients. J Anaesthesiol Clin Pharmacol. 2010;26:149–53.
19. Breschan C, Krumpholz R, Likar R, Kraschl R, Schalk HV. Can a dose of 2 microg.kg(-1) caudal clonidine cause respiratory depression in neonates? Paediatr Anaesth.1999;9:81-3.
20. Bouchut JC, Dubois R, Godard J. Clonidine in preterm-infant caudal anesthesia may be responsible for postoperative apnea. Reg Anesth Pain Med. 2001;26:83-5.
21. Aantaa R, Scheinin M. Alpha2-adrenergic agents in anaesthesia. Acta Anaesthesiol Scand. 1993:37:433-48,
22. Anand VG, Kannan M, Thavamani A, Bridgit MJ. Effects of dexmedetomidine added to caudal ropivacaine in paediatric lower abdominal surgeries. Indian J Anaesth. 2011;55:340–6
23. Bimbaumer L, Abramowitz J, Brown AM. Receptor-effector coupling by G proteins. Biochim Biophys Acta 1990;1031:163-224.
24. Tamsen A, Gordh T. Epidural clonidine produces analgesia. Lancet 1984; 2:231.
25. Dipak L Raval, Karthik N: A comparative study between dexmedetomidine and clonidine used as adjuncts to bupivacaine for postoperative analgesia by caudal route in pediatric patients. Asian Pac. J. Health Sci 2014;1(2):131-136