Postoperative Analgesia in Paediatric Patients: Comparative Study among Local Anaesthetics (Ropivacaine 0.25%), Opioids (Tramadol), A2 Agonist (Dexmedetomidine) Used in Caudal Block.

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Abstract:

Background: *The society of Paediatric Anaesthesia, on its 15th annual meeting at New Orleans, Louisiana (2001) clearly defined the alleviation of pain as a "basic human right", irrespective of age, medical condition, treatment, primary service response for the patient care or medical institution.[1] Finely et al observed that many types of so called "minor" surgery (e.g. circumcision) can cause significant pain in children.[2]*

One of the most commonly used regional anaesthetic techniques in paediatric surgeries is the caudal epidural block. Its main disadvantage remains the short duration of action. Hence, different additives have been used. Dexmedetomidine is a potent as well as highly selective α2 adrenergic receptor agonist. The aim of this randomized, double-blinded, study was to compare the duration of postoperative analgesia of caudal dexmedetomidine versus tramadol in combination with ropivacaine in paediatric patients undergoing lower abdominal or perineal surgery.

Patients and Methods: *A total of 60 paediatric patients, 1-6 years old and the American Society of Anaesthesiologists status I, II scheduled for lower abdominal and perineal surgeries were included in the study. The patients were enrolled into 3 equal groups: Group R patients (n = 20) received plain ropivacaine (0.25%) while Group RT patients (n = 20) received tramadol with ropivacaine, Group RD patients (n = 20) received dexmedetomidine with ropivacaine. Patients were placed in a supine position then inhalational general anaesthesia was induced, and laryngeal mask airway (LMA) was placed. Patients were then given caudal epidural analgesia. By the end of surgery reversal of muscle relaxation was done and the LMA was removed. Behaviour during emergence was rated with a 4-point scale, sedation with Ramsay's sedation scale, and pain assessed with face, legs, activity, cry, consolability (FLACC) pain score.*

Results: *The current study showed that minor complications were recorded in the post-anaesthesia care unit; in addition, significantly longer periods of analgesia and sedation were detected in Group RT and RD. The difference between the means of mean sedation score, emergence behaviour score, mean emergence time was statistically highly significant (P<0.001). The peri-operative hemodynamics were stable among the three groups.*

Conclusion: *The present study suggested that use of dexmedetomidine, during single dose injection, as an additive to the local anaesthetic ropivacaine in caudal epidural analgesia prolongs the duration of post-operative analgesia following lower abdominal as well as perineal surgery compared with caudal tramadol with no side-effects on the vital signs.*

Keywords: *Ropivacaine, caudal block, dexmedetomidine, tramadol, postoperative analgesia*

I.   Introduction

Being unpleasant, pain is a subjective sensation, which in children can only be experienced and not expressed, because they depend on their care-givers for their well-being.[1,2] Over the recent years, the concept of providing adequate post-operative analgesia in paediatric patients is well established, however, various methods showed side-effects limiting their use such as respiratory depression with IV opioids.[3] With a high success rate, caudal analgesia was proved to be a simple and effective technique in children. Caudal block is usually placed after the induction of general anaesthesia and is used as an adjunct to both intraoperative and postoperative analgesia in children undergoing surgical procedures below the level of the umbilicus. Caudal analgesia could reduce the amount of inhaled and intravenous (IV) anaesthetic administration, attenuate the stress response to surgery, facilitate a rapid, smooth recovery, and provide good immediate postoperative analgesia.[4, 5]

In spite of using long acting local anaesthetics, the main disadvantage of caudal analgesia remains the relatively short duration of action.[6] The use of caudal epidural catheter was a suggested solution to administer a continuous infusion or repeated top up doses, but concerns are available regarding the risk of infection. Hence different additives have been used in order to improve the duration of action as well as the quality of analgesia

of the local anaesthetic used in the single shot caudal block technique such as opioids, epinephrine, clonidine, ketamine and neostigmine.[5, 7, 8]

Dexmedetomidine is a potent as well as highly selective α2 adrenergic agonist having a sedative, sympatholytic and analgesic effect and have been described as a safe and effective additive in many anaesthetic applications and analgesic techniques.[9] It has, as much as, eight folds more stronger affinity to α2 adrenergic receptors and lower affinity to α1 receptors than clonidine, besides its great advantage in having higher selectivity to $α_{2A}$ adrenergic receptors, responsible for the analgesic effect of such drugs, compared with clonidine.

Tramadol was developed by the German pharmaceutical company Grünenthal GmbH in the late 1970s and marketed under the trade name Tramal. As an analgesic it's equipotent to meperidine without any respiratory depressant action. The most commonly reported adverse drug reactions are nausea, vomiting, sweating and constipation. Drowsiness is reported, although it is less of an issue than for opioids.[11, 12]

Ropivacaine, a long-acting amide local anaesthetic related structurally to bupivacaine, has been used for paediatric caudal anaesthesia. It provides pain relief with less motor blockade and is less cardio toxic than bupivacaine, which makes it a more suitable agent for caudal epidural analgesia, especially following day care surgery.[10] The aim of this randomized, double-blinded, study was to compare the duration of post-operative analgesia, sedation, as well as the incidence of any side effect of single dose caudal dexmedetomidine versus tramadol in combination with ropivacaine in paediatric patients undergoing lower abdominal or perineal surgery.

II.   Patients And Method

After obtaining approval from the Clinical Research Ethics Committee and obtaining informed and written consent from the parents or guardian, a total of 60 paediatric patients within the age range of 1 and 6 years, The American Society of Anaesthesiologists (ASA) physical status I, II of both sex scheduled for lower abdominal surgeries (table 3) were included in the study. The patients were randomized in a double blinded fashion using closed envelop method to get enrolled into 3 equal groups:

Group R patients (*n* = 20) received single dose caudal epidural analgesia using ropivacaine (0.25%) 1 ml/kg +0.9% saline (NS) to keep a constant volume of drug in all three groups.

Group RT patients (*n* = 20) received single dose caudal epidural analgesia using ropivacaine (0.25%) 1 ml/kg and tramadol 2mg/kg.

Group RD patients (n=20) received single dose caudal epidural analgesia using ropivacaine (0.25%) 1 ml/kg and dexmedetomidine 2µg/kg.

The volume was kept constant by dilution with NS.

Exclusion criteria included history of mental retardation or delayed development that may interfere with pain intensity assessment, known or suspected coagulopathy, any congenital anomalies of the sacrum, any infection at the site of injection, known or suspected allergy to any of the studied drugs.

Double blind study

Anaesthesiologist who administered the drug and the observer were blinded to the study. Sterile syringes containing equal volumes of drug or placebo were loaded by another anaesthesiologist not concerned or participating in the study. The intraoperative monitoring and postoperative observation was done by the same anaesthesiologist who administered the drug or placebo, but was unaware of the content of the syringes.

Pre-op evaluation

In all children, age, body weight, and baseline vital parameters were recorded. History regarding previous anaesthesia, surgery, any significant medical illness, medications and allergy was recorded. Complete physical examination and airway assessment were done. The following laboratory investigations were done: haemoglobin percentage, blood sugar, urea, serum creatinine and urine analysis.

All patients were premedicated with midazolam 0.5mg/kg and 0.01 mg/kg atropine I.M. 30 min before shifting to OR. Patients were kept fasting according to the ASA guidelines for water 2 h, breast milk 4 h, and infantile formula or light meals for 6 h. On arrival to the operating theatre, the standard monitors were applied including non-invasive blood pressure, electrocardiography and pulse oximetry. Induction of anaesthesia was achieved with 50% N2O and 8% sevoflurane in oxygen in spontaneous ventilation. An appropriate-sized laryngeal mask airway (LMA) was inserted. After the insertion of LMA, sevoflurane concentration was reduced to 3% in 50% nitrous oxide, patients were left in spontaneous ventilation. The inhaled concentration of sevoflurane was adjusted to achieve haemodynamic changes less than 30% of the baseline values. No other narcotics, analgesics or sedatives were used intraoperatively. Thereafter, patients were placed in a lateral position and the skin of the back over the sacrum was scrub using povidone iodine solution, and under strict aseptic precautions single dose caudal epidural injection was done using 25 G needle. Proper position of the needle was confirmed by the pop sensed during penetration of the sacro-coccygeal ligament, which was followed by the whoosh test[13, 14] done using 0.5 ml of air. After needle insertion and negative aspiration of blood

or cerebrospinal fluid, patients of Group R patients ($n = 20$) received ropivacaine(0.25%) 1 ml/kg +0.9% saline (NS) to keep a constant volume of drug in all three groups, group RT patients ($n = 20$) received ropivacaine (0.25%) 1 ml/kg and tramadol 2mg/kg, group RD patients (n=20) received single dose caudal epidural analgesia using ropivacaine (0.25%) 1 ml/kg and dexmedetomidine 2µg/kg. The volume was kept constant in all three groups by dilution with NS.

Standard monitoring was used during anaesthesia and surgery. Heart rate (HR), mean arterial pressure (MAP) and oxygen saturation (SpO2) were recorded before surgery and every 5 min till the end of surgery. The occurrence of intraoperative hypotension requiring a fluid bolus, bradycardia requiring atropine, and the maximum maintenance concentration of sevoflurane (%) were recorded. Behaviour during emergence was rated on a 4-point scale: [15, 16]

1) calm;
2) not calm but could be easily calmed;
3) not easily calmed, moderately agitated or restless; and
4) combative, excited, or disoriented.

Using the paediatric observational face, legs, activity, cry, consolability (FLACC) pain score[17] with its 0–10 score range, each patient's pain intensity was assessed at the end of surgery and then every 4 hours for 24 hours after operation. If the FLACC pain score was 4 or more, syrup paracetamol 15 mg/kg was administered. The duration of analgesia (from the time of caudal injection to the time at which FLACC score was 4 or more) was also recorded. For children less than 3 yrs Wong Baker pain score was used.

Wong Baker Pain Scale

0	1	2	3	4	5
No Hurt	Hurts Little Bit	Hurts Little More	Hurts Even More	Hurts Whole Lot	Hurts Worst

Table 1: Flacc Score

Parameter	Finding	Points
Face	No particular expression or smile	0
	Occasional grimace or frown withdrawn, disinterested	1
	Frequent to constant quivering chin, clenched jaw	2
Leg	Normal position or relaxed	0
	Uneasy restless tense	1
	Kicking or legs drawn up	2
Activity	Lying quietly, normal position, moves easily	0
	Squirming, shifting back and forth, tense	1
	Arched rigid or jerking	2
Cry	No cry (awake or asleep)	0
	Moans or whimpers occasional complaints	1
	Crying steadily, screams or sobs, frequent complaints	2
Consolability	Content relaxed	0
	Reassured by occasional touching hugging or being talked to, distractable	1
	Difficult to console or comfort	2

FLACC: Face, legs, activity, cry, consolability

Sedation score was assessed using Ramsay's sedation scale as follows: [18]
1. anxious and agitated or restless or both
2. co-operative, oriented, and calm
3. responsive to commands only
4. exhibiting brisk response to light glabellar tap or loud auditory stimulus
5. exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6. unresponsive
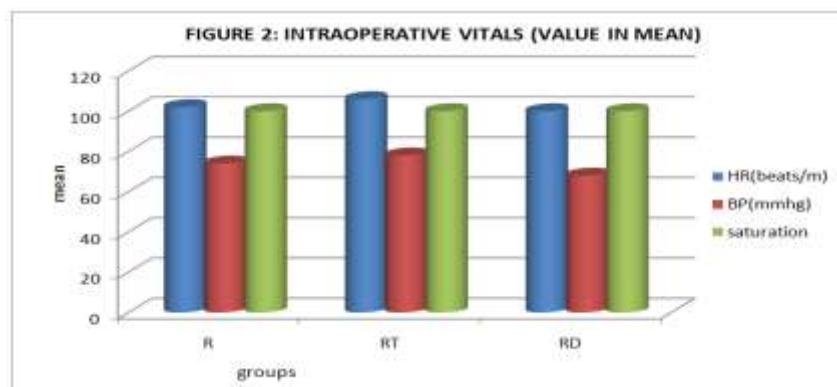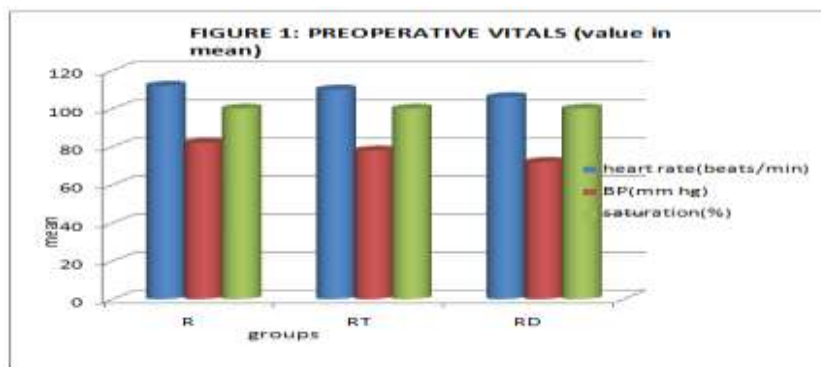
The following were also recorded:
1. The anaesthesia time (time from induction of anaesthesia to the end of surgery when sevoflurane was discontinued).
2. Time from caudal block to skin incision.
3. Time from caudal block to end of surgery.
4. Emergence time (time from the end of surgery to opening the eyes on calling).

Complications such as postoperative nausea and vomiting (PONV), respiratory depression, urinary retention, hypotension and bradycardia were also noted. Respiratory depression was defined as a decrease in SpO_2 of less than 95% requiring supplementary oxygen. Hypotension was defined as systolic arterial pressure 70 plus twice the age in years and associated with altered peripheral perfusion. Bradycardia was defined as HR below 80 beats /min for age 1 year and 60 beats/min for ages above 1 year.

Delayed anaesthetic emergence was defined as 20 min elapsing from the end of surgery to exiting the operating theatre. Failure of caudal block was defined as any increase in HR or MAP more than 20% of the pre-incision values. In our study, we did not encounter any failure of block as it was performed by consultants.

Statistical analysis

We calculated that 18 patients in each group would be needed to detect an intergroup difference in the average time to first rescue analgesic of at least 20% ($\alpha = 0.05$, $\beta = 0.9$). The sample size was increased to 20 patients in each group. Data were analyzed using SPSS for windows 12.0 (Chicago, IL, USA). Numerical variables were presented as mean ± standard deviation or median (95% confidence interval) and categorical variables were presented as frequency (%). One-way analysis of variance was used for between-group comparisons of numerical variables, if its assumptions were fulfilled, otherwise for non-parametric; the Kruskal-Wallis test was used. Tukey's honestly significant difference test or the Mann–Whitney test was used, whenever appropriate, as *post hoc* tests. Chi-square test (x^2) was used for between-group comparisons between categorical variables. A *P* value of 0.05 was considered statistically significant.

FIGURE 1: PREOPERATIVE VITALS (value in mean)

FIGURE 2: INTRAOPERATIVE VITALS (VALUE IN MEAN)

Results

The incidence of complications in PACU after recovery revealed that only one patient in group R and 3 patients in gp RT had incidence of nausea and vomiting. Two patients in group RT developed itching whereas the incidence was none in gp R or RD.

One patient each in all three groups had SpO_2 less than 95%, with no clinical significance or signs of hypoxia.

Table 2: Demographic Data

		Gp R	Gp Rt	Gp Rd
1	Age	3.5±2.1	3.6±1.1	3.8±0.8
2	Gender(M/F)	16/4	18/2	16/4
3	Body Weight	13.4±2.11	12.68±1.28	12.7±2.8
4	Duration Of Surgery	70±18.1	68.2±11.1	66.34±20.1

Table 3: Types Of Surgery

		R(N=20)(%)	Rt(N=20)	Rd(N=20)
1	Inguinal Hernia	4(20)	5(25)	4(20)
2	Hypospadias	2(10)	4(20)	2(10)
3	Undescended Testis	1(5)	1(5)	2(10)
4	Urethroplasty	6(30)	5(25)	3(15)
5	Rectal Polyp	4(20)	2(10)	4(20)
6	Circumcision	3(15)	3(15)	5(25)

Two patients developed urinary retention in gp RT with no incidence in group R or RD. There was only one incidence of laryngospasm/bronchospasm in gp R but it was not statistically significant, and was handled successfully with no complications.

The duration of postoperative analgesia was 6 ±2.1hrs in gp R, 10.23 ±0.56 hrs in gp RT and 17.24± 1.11 hrs in RD with a p value <0.001. There was a significant difference between the groups in FLACC score (figure3) measured 4 hrly in postoperative period. Gp R patients received significantly higher FLACC scores compared with gp RT which in turn were further higher than gp RD. In gp RT 15 patients i.e.75% achieved a FLACC score of 4 at 6th hr compared with 0 in both gps RT and RD. In gp RT, FLACC of 4 was achieved at 16th hr.

FIGURE 3: CHANGES IN PAIN SCORE ALONG WITH TIME (FLACC SCORE)

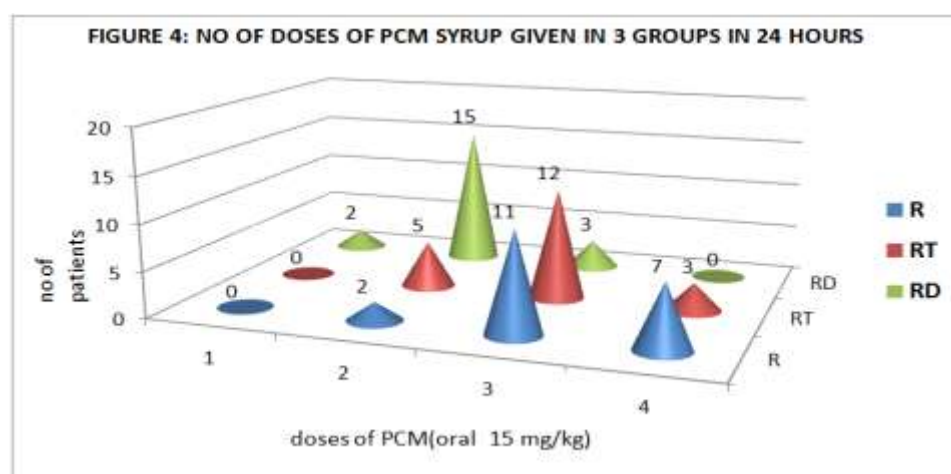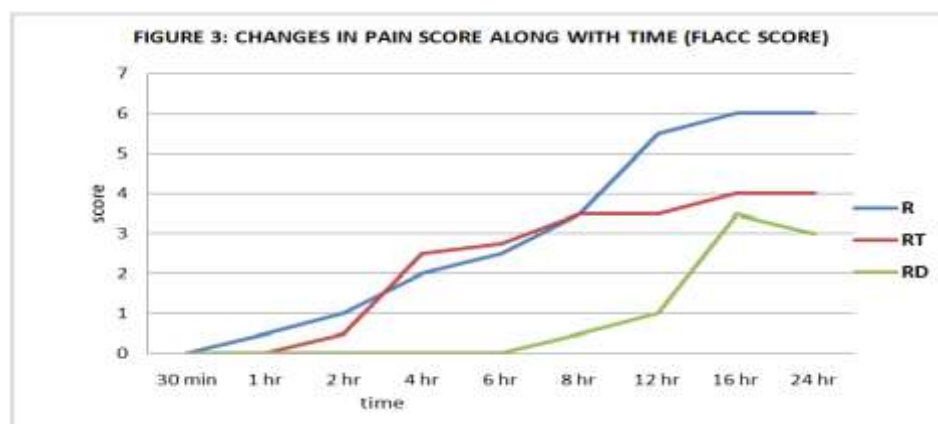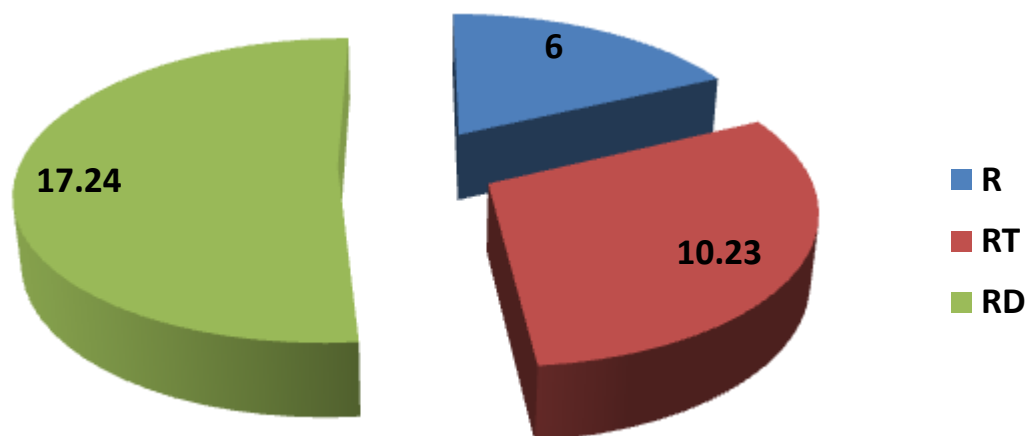FIGURE 4: NO OF DOSES OF PCM SYRUP GIVEN IN 3 GROUPS IN 24 HOURS

FIGURE 5: DURATION OF ANALGESIA (IN HRS)

FIGURE 6: DURATION OF SEDATION (IN HRS)

FIGURE 7: EMERGENCE TIME AND SCORE

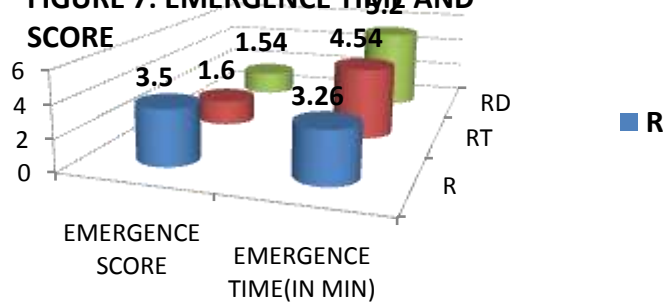| Table 4: Side Effects				
		R	Rt	Rd
1	Nausea/Vomiting	1	3	0
2	Hypotension	0	1	1
3	Bradycardia	0	0	0
4	Itching	0	2	0
5	Urinary Retension	0	2	0
6	Hypoxia (Spo$_2$ <95%)	1	1	1
7	Laryngo/Bronchospasm	1	0	0

The difference in mean sedation score among the 3 gps was highly significant (<0.001). RD gp had significant sedation as compared to R and RT, which means that RD gp children were asleep but easily arousable. The difference between emergence behaviour score between gp R and RT, RD gps was statistically highly significant with emergence score of 3.5 ±0.5 in gp R, 1.6±0.86 in gp RT, 1.54± 0.05 in gp RD (figure 7). Thus though the patients in gp RT and RD were calm and cooperative at the time of emergence from GA but in gp R were highly restless and agitated.

The mean emergence time in gp RD was much higher than other 2 gps being 5.2±1.36 minutes and that in gp RT was 4.54± 1.61 minutes and gp R was 3.26 ± 0.24 minutes. The difference of means among all 3 gps was statistically highly significant (p <0.001).

III. Discussion

Ropivacaine, in comparison to bupivacaine, has a wider margin of safety, less motor blockade, less cardiovascular or neurological toxicity and similar duration of analgesia. It can be safely used for regional anaesthesia and analgesia in the ambulatory setting in paediatrics.

Like clonidine,[19, 20] dexmedetomidine also enhances the effects of local anaesthetics without increasing the incidence of side effects. Dexmedetomidine compared to clonidine is a much more selective a2-adrenoceptor agonist, which might permit its application in relatively high doses for sedation and analgesia without the unwanted vascular effects from activation of a1-receptors. It is unique that its sedative effect can be reversed by atipamezole.[21, 22] The preferred route of administration of dexmedetomide is the intravenous (IV) route, although others have been studied.

One of the major advantages of dexmedetomidine over other sedatives are that the respiratory rate, carbon dioxide (CO_2) tension, and oxygen saturation are generally maintained during dexmedetomidine sedation in children. Dexmedetomidine provides an interesting quality of sedation that permits arousal with gentle stimulation. It has been studied for sedation in children for a number of different purposes, including radiologic procedures such as magnetic resonance imaging (MRI).[24-26]

In the present study, we found that the use of dexmedetomidine, during single dose injection, as an additive to the local anaesthetic ropivacaine in caudal epidural analgesia prolongs the duration of postoperative analgesia following lower abdominal as well as perineal surgery compared with caudal tramadol; furthermore, the duration of sedation was found to be longer with dexmedetomidine than with tramadol with no side-effects on the vital signs, or rescue analgesia requirement. However, the emergence time from anaesthesia and the condition of patients during recovery showed no difference. Postoperative side effects, including vomiting, itching and respiratory depression, were recorded in the PACU more with tramadol rather than dexmedetomidine.

Caudal epidural analgesia is a widely used technique for providing regional anaesthesia and analgesia in children undergoing infra umbilical and lower limb surgeries and to prolong its effect wide range of additives have been used in combination with local anaesthetics to promote analgesia.[21, 22] The use of additives during caudal anaesthesia have increased in the last decade by 58%, specially with ketamine 38% and clonidine 42%, whereas the use of opioids as additives has decreased from 36% to 18% due to the higher incidence of side-effects as nausea and vomiting, itching and respiratory depression specially in children.[23]

Supporting the results of the present study was the results of El-Hennawy et al, who compared the use of single dose caudal epidural injection of dexmedetomidine or clonidine or placebo (normal saline) added to bupivacaine, and proved that the duration of analgesia was found to be significantly prolonged with dexmedetomidine, and to a lesser extent with clonidine than with plain bupivacaine, without any increase in the incidence of side-effects.[27] Furthermore Demiraran et al in their study on the use of single dose epidural morphine versus tramadol for postoperative analgesia in pediatric surgery showed that the incidence of side effects as respiratory depression, itching, skin rash and vomiting was higher with morphine.[28] Neogi et al studied the effect of caudal dexmedetomidine added to ropivacaine 0.25% against caudal clonidine with ropivacaine for postoperative analgesia in children and found out that the duration of analgesia was prolonged for both drugs when compared with ropivacaine alone with good hemodynamic stability moreover, they detected no side-effects for both drugs.[29]

In another study performed by Anand et al they studied the effect of adding dexmedetomidine to caudally injected ropivacaine on the intensity of postoperative analgesia, and its safety in the children performing abdominal surgeries, and their results indicated that dexmedetomidine achieved a remarkable relief of post-operative analgesia leading to better quality of sleep and minimal agitation during recovery from anaesthesia, but unlike the present study, they reported a prolonged postoperative sedation.[30]

In our study, we found that by adding tramadol 2mg.kg^{-1} to caudal ropivacaine (0.25%) 01ml.kg^{-1} in children undergoing sub-umbilical operation, significantly increased the duration of pain free period post-operatively. Similar results were reported by Gune et al during a study of children undergoing hypospadias repair showed that caudal tramadol provides better and longer lasting postoperative analgesia than i.v tramadol.[31] Senel et al in

a study on children undergoing herniorrhaphy showed that, caudal administration of bupivacaine with the addition of tramadol resulted in superior analgesia with a longer period without demand for additional analgesics compared with caudal bupivacaine and tramadol alone without an increase of side effects.[32]

The incidence of emergence agitation, which is frequently seen during recovery from inhalational anaesthesia in children, were much less in children with preoperative caudal block in all three groups and it was more less in RT and RD groups and this is supported by a previous study of Weldon et al who reported that effective postoperative analgesia may reduce the incidence of emergence agitation with sevoflurane anaesthesia.[33] The degree of sedation was comparable in two groups. The potency of single shot caudal bupivacaine was increased by addition of dexmedetomidine and tramadol because in our set up it was neither technically possible nor cost effective to use caudal epidural catheter and maintain postoperative analgesia with bupivacaine alone. A prolonged and effective postoperative analgesia to children means a cooperative child with less emotional and hemodynamic stress and rapid recovery with less hospital stay. Mean duration of postoperative analgesia with caudal ropivacaine was 6 hrs whereas with addition of tramadol it increased up to 10.5 hrs, with dexmedetomidine upto 18 hrs, without increasing the dose as well as the side effects of ropivacaine as it was shown in various studies. A higher dose of tramadol could have caused nausea and vomiting, similarly higher dose of dexmedetomidine could have caused hypotension and bradycardia whereas increasing the dose of ropivacaine could have caused more motor weakness and urinary retention.

On the contrary to our study, Singh et al compared the use of caudal clonidine versus morphine with bupivacaine, and showed a longer duration of analgesia as well as sedation with morphine in paediatric patients undergoing upper abdominal surgery than the duration in the present study, in addition to, a lower incidence of post-operative complications than the results of the present study.[34] Moreover, Luz et al in their study of the effect of clonidine versus morphine added to bupivacaine when given caudally to improve postoperative analgesia in children undergoing lower abdominal surgery as orchidopexy, they suggested that the duration of analgesia achieved postoperatively was comparable between both drugs with no significant difference, and this may be explained by the use of the higher selective α2 agonist dexmedetomidine in the present study beside using it in a higher dose (2 μg/kg).[35] However supporting the results of the current study was that of Nasr and Abdelhamid and Saadaway et al, who studied the effect of caudal dexmedetomidine versus fentanyl with bupivacaine on the stress response and post-operative analgesia in paediatric cardiac surgery, and found that dexmedetomidine attenuated the stress response and produced better analgesia.[36,37] Lastly, our study had its limitations. Firstly double blinding could not be possible in a few cases. The doses of drugs were selected on basis of previous studies and more studies are required to confirm the highest dose possible. In some children proper pain assessment was very difficult and therefore only estimates could be done.

IV.   Conclusion

The present study suggested that use of dexmedetomidine, during single dose injection, as an additive to the local anaesthetic ropivacaine in caudal epidural analgesia prolongs the duration of post-operative analgesia following lower abdominal as well as perineal surgery compared with caudal tramadol with no side-effects on the vital signs. Postoperative side effects were seen with caudal tramadol injection rather than with dexmedetomidine.

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