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COMPARISON BETWEEN CLONIDINE AND DEXMEDETOMIDINE AS AN ADJUVANT TO BUPIVACAINE AS AN ANALGESIC FOR CAUDAL ANALGESIA IN PAEDIATRIC PATIENTS

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ABSTRACT

To compare onset and duration of analgesia and to study side effects of clonidine and dexmedetomidine as an adjuvant to bupivacaine in caudal block. 90 paediatric patients belonging to ASA I&II were randomly allocated to receive caudal analgesia.30 patient in each group. Group B: Inj. Bupivacaine 0.25 %(1 ml/kg) with 1 ml NS, Group C: Inj. Bupivacaine 0.25 %(1 ml/kg) with clonidine 1µ/kg in 1 ml NS, Group D Inj. Bupivacaine 0.25 %(1 ml/kg) with dexmedetomidine 1 µ/kg in 1 ml NS. All patients were observed for duration of analgesia, sedation score, heart rate and blood pressure. Postoperative pain was assessed by using FLACC pain score & sedation by sedation score. Patients were observed up to 24 hours. The duration of analgesia were significantly decreased in group C & D compared to group B. Haemodynamic stability is better with group C & D. Duration of postoperative analgesia was longer with group D compared to group C & B. Bupivacaine with dexmedetomidine in caudal analgesia has longer duration of postoperative analgesia and better hemodynamic stability compared to bupivacaine with clonidine or bupivacaine alone. It is useful as an adjuvant to general anaesthesia or as a sole technique with less side effects and high success rate.

Key words: Clonidine, Dexmedetomidine, Caudal analgesia, Bupivacaine, Paediatric patients.

INTRODUCTION

Caudal epidural analgesia is one of the most popular regional blocks in paediatric anaesthesia. Caudal block is a useful alternative/supplement to general anaesthesia and total I.V. anaesthesia as it provides effective post-operative analgesia[1-3]. One of the main drawbacks of caudal technique is short duration of analgesia even with long duration local anaesthetics like bupivacaine and ropivacaine.

Various additives e.g. Ketamine, Neostigmine, Clonidine, Dexmedetomidine, Ephedrine, and opioids have been used to prolong the duration of analgesia provided by single injection. Ketamine has potential risk of neurotoxicity and opioids have side effects such as nausea, vomiting and respiratory depression. Clonidine, an alpha 2 agonist, widely used as an antihypertensive agent in 70s and 80s, is now used as sedation, premedication and as adjuvant analgesic [4]. Its addition allows use of lower concentration of local anaesthetic for achieving same level of anaesthesia but with a prolonged duration of analgesia, thus increasing margin of safety and reducing incidence of motor block. Because of its sedative and analgesic effects, it is gaining popularity in anaesthesiology. It does demonstrate adverse effects like sedation, hypotention and bradycardia. Dexmedetomidine, highly selective for alpha 2 receptors, has been used as an adjuvant to local anaesthetics in caudal block and mediate its analgesic and sedative effects. Duration of analgesia is found to be prolonged with dexmedetomidine without any serious adverse effects [5].

Considering the above facts, we designed the present study using bupivacaine alone and with adjuvants, clonidine and dexmedetomidine, in caudal epidural block

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in order to assess duration of postoperative analgesia, hemodynamic changes, side effects and degree of sedation.

MATERIAL AND METHODS

This study was carried out after obtaining permission from institutional ethical committee and obtaining written informed parental consent. We recruited total 90 patients, ASA physical status I-II,age 6 months to 12 years, undergoing subumbilical surgeries under general anaesthesia for our prospective randomized controlled study. Children with sacral bone abnormality, spina bifida, coagulopathy and infection at the site of caudal injection were excluded from our study.

The patients were assigned randomly into three groups, 30 patients in each group

Group B: Control group- Bupivacaine 0.25 % (1ml/kg) with normal saline 1 ml

Group C: Clonidine group- Bupivacaine 0.25 % (1ml/kg) with clonidine 1mcg/kg in 1 ml normal saline

Group D: Dexmedetomidine group- Bupivacaine 0.25 % (1ml/kg) with dexmedetomidine 1 mcg/kg in 1 ml normal saline

The patients underwent a pre-anaesthetic check-up the day before surgery and all the routine and specific investigations were noted. Patients were kept fasting for 4 hours. After arrival in operating room, monitoring which included ECG, pulse oximetry, NIBP were applied and baseline values were recorded. Intravenous cannula was inserted into a suitable vein and inj. Isolyte P was started.

PROCEDURE

Inj. Glycopyrrolate (4 µg/kg) IV was given as premedication. Pre-oxygenation was done by a facemask and JR circuit with fresh gas flow of 6 L/min oxygen. Anaesthesia was induced with Inj. Sodium thiopentone 4-5 mg/kg i.v. and Inj. Succinylcholine 1.5-2 mg/ kg i.v. After intermittent IPPV, trachea was intubated with appropriate ET tube/ LMA. Maintenance of anaesthesia was done by Oxygen, Nitrous Oxide, Sevoflurane. Inj.Atracurium (0.5 mg/kg) i.v. was given as a muscle relaxant. Intravenous fluid was given according to weight and estimated fluid loss depending on type of surgery. No other narcotics, analgesics, sedatives, or antiemetics were administered intra-operatively.

CAUDAL TECHNIQUE

After induction, patients were placed in the lateral decubitus position, and a single dose caudal block was performed under aseptic and antiseptic conditions using a 23G hypodermic needle and standard loss of resistance technique. The drugs were given in caudal block according to the groups after negative aspiration for blood and cerebrospinal fluid.

The site of injection was dressed and the patient was turned supine. Maximum volume limit was 20 ml for all three study groups. Haemodynamic parameters (heart rate, ECG, blood pressure), respiratory rate, ETCO2 and SPO_2 were recorded before induction, after induction and then immediately after caudal anaesthesia, and every 10 minutes during surgery. Duration of anaesthesia (time from induction of anaesthesia to the time of extubation), duration of surgery; and duration of postoperative analgesia,(time from single shot caudal injection of drug to the FLACC pain score of more than 4) were also noted. A decrease in MAP >30% was defined as hypotension and was treated with intravenous fluids. Perioperative blood loss was replaced meticulously using crystalloids and blood, as appropriate. Perioperative bradycardia defined as heart rate below 80/min for age less than 1 year and less than 60/min for age above 1 year was treated with Inj. Atropine 0.01 mg/kg. At end of surgery, neuromuscular block was reversed with Inj. Glycopyrrolate 8 µg/ kg and Inj. Neostigmine 0.05 mg/ kg. Trachea was extubated after oral and endotracheal suction/ LMA removed. Pulse, blood pressure, SpO_2, respiratory rate, sedation score, FLACC score were recorded postoperatively at 0 minutes, 15 minutes, 30 minutes and every 30 minutes for next 6 hour and then every 1 hour for next 6 hours in post-operative care unit.. Postoperative respiratory depression, defined as oxygen saturation less than 95 % was treated by oxygen with ventimask at the rate of 4 L/minute. Postoperative nausea and vomiting were treated with i.v. ondansetron 0.06 mg/kg. Postoperative pruritus was treated with i.v. diphenhydramine 0.2 mg/kg. Patients were assessed for 24 hours postoperatively. Analgesia was assessed using FLACC pain scale and sedation was assessed by sedation score. Children who had a pain score of more than 4 were administered Acetaminophen 15 mg/kg suppository.

FLACC score

	0	1	2
Face	No expression or smile	Occasional grimace or frown, Withdrawn, uninterested	Freq to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tensed	Kicking or legs drawn up
Activity	Lying quietly normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, jerky
Cry	No cry (awake or asleep)	Moans or whimper, occasional complaint	Crying, steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

Sedation score : 0. Eyes open spontaneously; 1. Eyes open in response to verbal command; 2. Eyes open in response to physical stimulation; 3. Unarousable

OBSERVATION AND RESULTS

Table 1. Demographic Data

Variables	Group B (n=30)	Group C (n=30)	Group D (n=30)	P value
Age(years) Mean± SD	4.43 ± 2.14	5.5 ± 2.48	5.26 ± 2.24	0.17
Weight(Kg) Mean± SD	12.87 ± 4.12	14.1 ± 4.22	14.13 ± 4.3	0.42
Sex ratio M:F	27:3	25:5	28:2	0.39

Table 1 shows all three groups were comparable in respect to age, weight and sex ratio without any significant difference ($p > 0.05$)

Table 2. Type of surgery

Surgery	Group B(No of Patients)	Group C (No of Patients)	Group D (No of Patients)
Inguinal hernia	2	3	4
Hypospadias & urethral fistula repair	20	17	16
Orchidopexy	2	3	4
Cystolithotomy	3	3	3
Extrophy bladder repair	3	4	3

Table 2 shows all three groups were comparable in respect to number of patients for given type of surgery without any significant difference ($p > 0.05$)

Table 3. Duration of surgery

Duration(min)	Group B	Group C	Group D	P value
Mean ± SD	78.67 ± 15.69	75.50 ± 20.65	83.5 ± 22.81	0.299

There was no statistically significant difference in duration of surgery in all three groups.($p>0.05$)

Table 4. Mean duration of caudal analgesia in hours

Mean duration of analgesia(Hours)	Group B	Group C	Group D	P-value
Mean±SD	4.51±0.99	8.02±1.02	8.385±1.24	0.001(B & C)
				0.001(B & D)
				0.224(C & D)

Table 4 and Fig-1 shows the mean duration of caudal analgesia in all three groups. This duration was significantly prolonged by addition of Clonidine and Dexmedetomidine to bupivacaine(group C & D) in comparison to bupivacaine alone(group B).There was statistically significant difference in duration of caudal analgesia between group B & group C and group B & group D ($p<0.05$).But there was no significant difference in duration of caudal analgesia between Clonidine (group C) and Dexmedetomidine (group D). ($p>0.05$)

Table 5. FLACC score at 1 hour

FLACC score (1 hour)	Group B	Group C	Group D	P-value
Mean ± SD	2.23±0.77	1.70±0.46	1.63±0.55	0.002 (B & C)
				0.001 (B & D)
				0.595 (C & D)

Table 6. FLACC score at 4 hours

FLACC score (4 hours)	Group B	Group C	Group D	P-value
Mean ± SD	4.40±0.85	2.83±0.38	2.66±0.48	0.001(B & C)
				0.001 (B& D)
				0.134 (C & D)

Table 7. Postoperative Mean Sedation Score

Time(Hours)	Mean Sedation score			P value	
	B group	C group	D group	(B & C)	(C & D)
0	1.87 ± 0.34	2.57 ± 0.50	2.63 ± 0.48	0.001	0.637
1	1.53 ± 0.57	1.83 ± 0.37	1.93 ± 0.24	0.019	0.219
2	0.83 ± 0.38	1.40 ± 0.49	1.63 ± 0.54	0.001	0.089
3	0.29 ± 0.46	1.23 ± 0.43	1.40 ± 0.43	0.001	0.217
4	0.08 ± 0.27	0.90 ± 0.30	0.96 ± 0.65	0.001	0.648

Mean sedation score immediately after postoperative period was higher in group C and group D. After 4 hours of awakening, there was gradual fall in mean sedation score in all three groups. There was slightly prolonged sedation in dexmedetomidine group(group D) in compared to clonidine group(group C) ($p>0.05$)

Table 8. Intraoperative Mean BP

Time(minutes)	Intraoperative Mean BP (mmHg)			P value
	B group	C group	D group	
0	87.73 ± 7.25	90.04 ± 5.64	89.47 ± 6.45	0.360
20	87.73 ± 7.25	90.04 ± 5.64	89.47 ± 6.45	0.360
40	87.13 ± 6.46	90.47 ± 5.27	88.20 ± 6.67	0.107
60	86.27 ± 5.91	90.00 ± 5.34	87.70 ± 7.09	0.066
80	86.21 ± 5.37	89.71 ± 5.64	87.10 ± 6.60	0.063
100	86.67 ± 3.05	84.00 ± 6.92	84.80 ± 4.14	0.109
120	85.70 ± 0.07	88.67 ± 9.01	89.60 ± 8.87	0.103

Table 9. Intraoperative Mean Pulse rate

Time(minutes)	Intraoperative Mean Pulse rate/min			P value
	B group	C group	D group	
0	117.47 ± 10.08	113.47 ± 9.69	111.50 ± 9.50	0.060
20	117.47 ± 10.08	113.47 ± 9.69	111.50 ± 9.50	0.060
40	113.80 ± 10.17	110.50 ± 11.16	107.86 ± 9.05	0.082
60	111.68 ± 9.56	109.45 ± 10.33	105.62 ± 9.82	0.062
80	109.79 ± 8.37	108.86 ± 10.07	104.65 ± 10.36	0.095
100	107.25 ± 8.61	109.00 ± 9.64	108.00 ± 7.87	0.739
120	111.00 ± 4.24	111.33 ± 12.85	111.20 ± 9.65	0.991

Intra-operative mean pulse rate and MAP shown that. In group C and D, there is slight fall in mean pulse rate after 30 minutes of caudal drug injection. There was no statistically significant difference in fall in pulse rate between group C and group D. ($p>0.05$)

Table 10. Postoperative Mean Pulse rate

Time(Hours)	Postoperative Mean Pulse rate			P value
	B group	C group	D group	
0	110.60 ± 7.48	109.20 ± 7.60	110.83 ± 9.00	0.699
1	106.73 ± 7.71	105.27 ± 8.98	107.27 ± 8.72	0.642
2	107.86 ± 6.94	105.60 ± 9.77	104.93 ± 8.55	0.380
3	107.33 ± 6.66	106.13 ± 8.58	106.20 ± 9.81	0.827
4	108.46 ± 5.54	107.33 ± 8.66	107.47 ± 9.74	0.844

Table 11. Postoperative Mean BP

Time(Hours)	Postoperative Mean BP			P value
	B group	C group	D group	
0	86.53 ± 5.45	88.47 ± 4.27	89.20 ± 6.35	0.154
1	87.87 ± 5.27	87.47 ± 4.92	85.80 ± 7.29	0.361
2	88.55 ± 6.54	87.53 ± 4.68	84.87 ± 7.33	0.070
3	90.83 ± 6.09	87.73 ± 4.72	86.13 ± 6.84	0.221
4	90.46 ± 5.10	89.13 ± 5.13	87.47 ± 6.51	0.125

In the post-operative period, BP and the pulse rate increased gradually towards the pre-operative values in all three groups. There was no statistically significant difference in BP and pulse rate between all three groups. ($p>0.05$).

Table 12. Postoperative complications

Post-op complication	Group B	Group C	Group D
Nausea & vomiting	1(3.3 %)	4(13.3%)	5(16.6%)
Bradycardia (<80/min for age<1 yr and<60/min for age>1 yr)[2]	0	1(3.3 %)	4(13.3%)
Respiratory depression (SPO_2< 93%)	0	0	0
Hypotension (decrease in MAP >30%)	0	0	0

Above table shows there was higher incidence of nausea and vomiting in group C and group D in compare to group B but difference was not statistically significant ($p=0.23$). No episodes of respiratory depression and hypotension were observed in any of three groups. Bradycardia was observed in group C and group D. Incidence of bradycardia was higher in group D compare to group C but not statistically significant ($p=0.16$).

Mean time to first micturation was recorded in all three groups. There was no statistically significant difference in mean time of first micturation among three groups. ($p > 0.05$)

Fig 1.

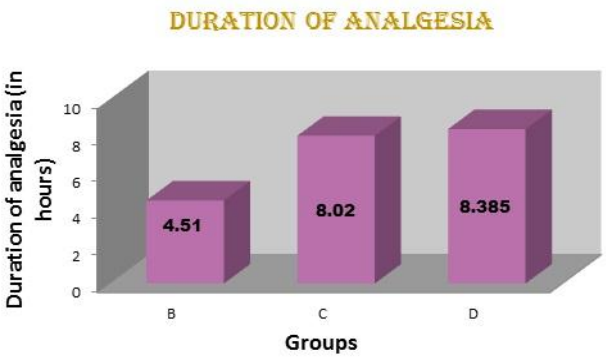


Fig 2.

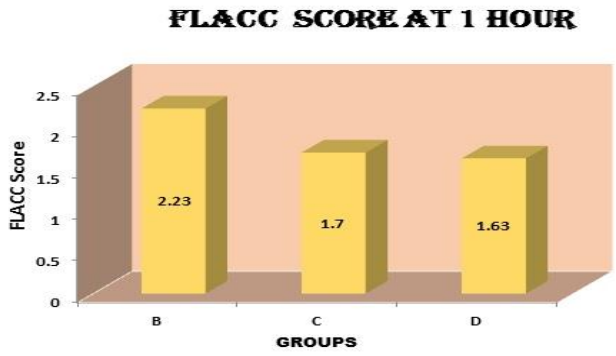
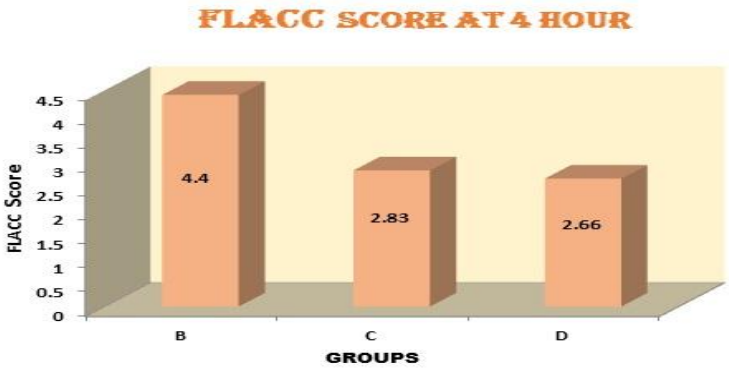


Fig 3.



Adding clonidine and dexmedetomidine significantly reduce the FLACC scores in group C & group D as compared to group B. Higher FLACC scores were observed in plain bupivacaine group (group B). There was statistically significant difference in FLACC scores between group B & group C and group B & group D ($p<0.05$).But there was no significant difference in FLACC scores between Clonidine (group C) and Dexmedetomidine (group D).($p>0.05$)

DISCUSSION

Caudal epidural anesthesia is a simple, frequently used technique, which provides very effective analgesia and postoperatively in paediatric patients undergoing infraumbillical surgeries like herniotomy, orchidopexy, hypospadiasis repair.

Postoperative analgesia provides not only pain relief but also inhibits trauma induced nociceptive impulses to blunt autonomic reflexes.it allows the patients to breath and move freely to enhance early restoration of function.[6]. Enteral and parental analgesics (both opioids and non opioids) used for providing postoperative analgesia, are associated with risks like gastro-intestinal bleeding, precipitation of asthma, nausea and vomiting, thrombocytopenia, 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 minimum of drug dose and complications. [7].

Sharpe et al speculated that a small volume of bupivacaine (0.5 ml/kg) may not be enough to deliver clonidine up to the spinal cord, leaving only direct action on the nerve routes in the caudal area. These findings suggest that the addiction of clonidine 2µg/kg to low volumes of caudal anaesthetics has limited clinical benefit in children undergoing circumcision. This was the reason we had chosen a standard dose of 1ml/kg of 0.25% bupivacaine as the final volume in all groups.[8]

There are several formula for determining the volume to anesthetic level relationship for caudal anesthesia in infants and children. Dalens and Hasnaoui recommend caudal volumes between 0.7 and 1 ml to achieve an adequate level of analgesia for inguinal surgery. The larger volume (1ml/kg) provided more satisfactory analgesia in infraumbilical surgeries.

Several adjuvants have been used to prolong the duration of analgesia of bupivacaine for caudal analgesia in children. opioids (e.g.morphine, butorphanol) ketamine, clonidine, midazolam, dexmedetomidine are added to bupivacaine to increase the duration of analgesia, decrease the individual dose of drug and thereby decreasing the side effects [9].

In our study we had used doses of clonidine 1µg/kg and dexmedetomidine1µg/kg. Neogi, bhattacharjee dp, dawn et al compared clonidine 1µg/kg and dexme detomidine 1µg/kg as adjuncts to ropivacaine 0.25% for caudal analgesia in paediatric patients and concluded that addition of both clonidine and dexmedetomidine with ropivacaine administered caudally significantly increases

the duration of analgesia.in our study we had also selected 1µg/kg dose of clonidine and dexmedetomidine [10].

Clonidine produce analgesia by interacting with alpha 2 adrenergic receptors, located on superficial laminae of spinal cord and brainstem nuclei implicated in pain. The dose of clonidine for caudal block is 1-5 µg/kg.we chose a dose of 1µg/kg in our study. Findings of Klimscha et al, showing that increasing the dose from 1µg/kg to 2µg/kg did not enhance the analgesic effect of clonidine but increase the incidence of side effects like respiratory depression, bradycardia and hypotension with increasing dose.[11]

Dexmedetomidine produce analgesia by acting on alpha 2 receptors in the locus ceruleus and dorsal horn of spinal cord having an eightfold greater affinity for alpha 2 receptors than clonidine and much less alpha 1 effects. Higher selectivity for alpha 2a responsible for the hypnotic and analgesic effects.[2] we also used dose of 1 µg/kg dose for our study. Neogi et al compared clonidine 1µg/kg and dexmedetomidine 1 µg/kg as adjuncts to ropivacaine 0.25% for caudal analgesia in paediatric patients and concluded that addition of both clonidine and dexmedetomidine with ropivacaine administered caudally significantly increases the duration of analgesia.[10]

We also wanted to keep uniform premedication in all children to avoid the confounding effects of the premedicant drug in assessment of postoperative analgesia. We chose the FLACC scale to evaluate pain post operatively as it is easy to use, validated and give us an objective evaluation.[12]. FLACC score 4 or more, rescue analgesic in form of acetaminophen suppositories 15 mg/kg was given in all three groups.

We chose to monitor our patients for a period of 24 hours post operatively.

In our study, duration of caudal analgesia (table 5) using plain bupivacaine (group b) was (mean ± S.D) 4.51 ± 0.99 hours, which increased by adding clonidine (group c) to(mean ± S.D) 8.02 ± 1.02 hours and dexmedetomidine (group d) to (mean ± S.D) 8.385 ± 1.24 hours. ($p < 0.05$, significant). Aruna Parameswari et al [13] in their study, the mean duration of analgesia was significantly longer in group-b (bupivacaine + clonidine) (mean ± S.D) 593.4 ± 423.3 minutes than in group- a (bupivacaine) (mean ± S.D) 288.7 ± 259.1 minutes. Children in group b had lower pain scores and requirement of rescue medications. Saadawy I et al [5] study which also suggested that addition of dexmedetomidine to bupivacaine significantly prolonged analgesia ($p<0.001$).

So in our study, there was significant difference in duration of caudal analgesia in plain bupivacaine compared to bupivacaine + clonidine and bupivacaine +dexme detomidine. But there was no significant difference in duration of caudal analgesia between clonidine and dexmed etomidine group. A.M.Hennaway et al study also suggested that, duration of caudal analgesia prolonged by adding clonidine and dexmedetomidine with bupivacaine [2].

In the immediate post- operative period sedation score was higher in the clonidine and dexmedetomidine groups. Patients were sedated but arousable. After four hours the mean sedation scores in both the groups was almost same and statistically not significant. Patients were not deeply sedated (unaruosable, score -3), during the study period. De negri p, ivani g, visconti cet alet al in their study also noted that postoperative sedation score was higher in clonidine and dexmedetomidine groups [14]

Hemodynamic variable during pre-op,intra-op and post-op between the groups were comparable and were not stastically significant and therapeutic interventions were not required.no episodes of clinically significant postoperative complications such as ponv, respiratory depression, urinary retention, pruritus, hypotension and bradycardia were observed. Joshi W et al also reported in their study that nausea - vomiting was seen more frequently in clonidine group.[2,5,10]

In our study, we had not observed decrease in respiratory rate and fall in spo2 requiring oxygen supplementation. We had also not observed incidence of hypotension. JJ Lee, Rubin AP et al in their study also noted that any incidence of respiratory depression and hypotension had not occur [15].

CONCLUSION

Hence, we find clonidine (1 µg/kg dose) and dexmedetomidine (1 µg/kg dose) are safe and effective adjuvant to bupivacaine in caudal block in paediatric patients. But addition of dexmedetomidine does not offer any significant advantage over clonidine without risk of side effects.

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