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Efficacy and safety of dexmedetomidine as an adjuvant to caudal levobupivacaine in paediatric patients

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Keypoints

A prospective, interventional study was performed amongst 60 children of aged 1-12 years to evaluate dexmedetomidine as an adjuvant to levobupivacaine to assess haemodynamic stability, analgesic efficacy and duration of postoperative analgesia, postoperative sedation and any adverse effects in children.

Abstract

Introduction

Caudal block is effective and safe technique for infraumbilical surgeries. Several adjuvants have been used to prolong the duration of caudal analgesia.

We have designed the study using dexmedetomidine as an adjuvant to levobupivacaine to assess haemodynamic stability, analgesic efficacy, and duration of postoperative analgesia, postoperative sedation and any adverse effects in children.

We studied the safety and efficacy of dexmedetomidine as an adjuvant to levobupivacaine in caudal analgesia in pediatric patients posted for herniotomy, orchiopexy and circumcision.

Materials and Methods

This is a prospective, interventional study conducted in 60 children of aged 1-12 years.

Patients were assigned randomly in two groups, Group L with 0.25% levobupivacaine and Group LD with 0.25% levobupivacaine and dexmedetomidine 1 μ/kg.

Total volume was 1 ml/kg for herniotomy and orchiopexy and 0.5 ml/kg for circumcision in both groups.

Postoperative analgesia and sedation was assessed by using FLACC (Face, legs, activity, cry, consolability) score and 4 point sedation score respectively upto 24 h postoperatively. Unpaired student's t-test and Mann-Whitney U test was used for statistical analysis.

Results

Addition of dexmedetomidine to caudal levobupivacaine significantly prolonged duration of analgesia up to 12.8 hours (p value <0.001). Group LD patients achieved statistically significant reduction in FLACC score and higher sedation compared with Group L. Perioperative haemodynamic were stable among both groups and no adverse effects were reported postoperatively.

Conclusion

Dexmedetomidine as an adjuvant to levobupivacaine is safe in paediatric patients and effectively reduces postoperative pain. However it may cause early postoperative sedation, yet without respiratory depression.

Keywords: levobupivacaine, dexmedetomidine, paediatric surgery, caudal anaesthesia.

Introduction

Caudal anaesthesia is a safe and effective mode of regional anesthesia used in paediatric patients for lower abdominal surgical procedures. This technique provides analgesia throught out surgical procedure, decrease in intraoperative stress, decrease in requirement of analgesic and anaesthetic agent and a good

postoperative analgesia.[1] The main disadvantage of this technique is the short duration of action after a single injection use of various adjuvants like epinephrine, opioid, ketamine and α_2 agonist has been investigated to prolong its duration of action.[2]

Levobupivacaine is a S(+) enantiomer of racemic bupivacaine and has similar local anaesthetic properties and potency.[3] It provides effective analgesia with less dense motor blockade.

It also has less cardiac and neurotoxic adverse effects than bupivacaine.[4] Dexmedetomidine is α_2 agonist and has higher affinity for α_{2A} receptors which is responsible for the hypnotic, analgesic and sympatholytic effects.[5] Duration of analgesia is prolonged with its use without significant haemodynamic or respiratory effects.[6]

Materials and Methods

This prospective, interventional, single centered randomized study was conducted at tertiary care hospital after approval from hospital ethical committee and departmental permission. Sixty paediatric patients with American Society of Anaesthesiologist (ASA) physical status group I-II, between one to twelve years of age, of either sex undergoing surgery like herniotomy, orchiopexy and circumcision were included.

Exclusion criteria were non consenting parents, known allergy to study drugs, history of developmental delay, neurological disease and skeletal deformity, suspected coagulopathy and infection at caudal block site.

Patients were assigned randomly into two groups, Group L (*n*=30) was taken as levobupivacaine 0.25% group and Group LD (*n*=30) as levobupivacaine 0.25% combined with dexmedetomidine 1 µg/kg.Total volume of drug for caudal block varied according to surgery and was 1 ml/kg for herniotomy and orchiopexy and 0.5 ml/kg for circumcision in both groups.

Routine preanaesthetic evaluation was performed. Investigations like complete blood count, urine-routine and microscopy and chest X-ray was recorded.

Study procedure including risks and benefits were explained to patient's guardian. On the day of surgery written informed consent was obtained from parents. Intravenous glycopyrrolate 4 µg/kg, midazolam 0.05 mg/kg and ketamine 1 mg/kg was given to patient prior taking to theatre.Patients were monitored by using standard ASA monitors like electrocardiography, non invasive blood pressure, pulse oximetry and capnography during anaesthesia. Baseline heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse oximetry reading were noted. Ringer lactate was started as a maintenance fluid according to holiday segar formula. After adequate preoxygenation patients were induced with intravenous propofol 2 mg/kg till loss of eye lash reflex and jaw relaxation. Anaesthesia was maintained with oxygen, nitrous oxide and sevoflurane and ventilation was controlled via face mask attached to JR (Jackson Rees) circuit. The inhaled concentration of sevoflurane was adjusted to achieve haemodynamic changes up to the 30% of baseline values (lower limit). No other narcotics, analgesic or sedatives were given intraoperatively. Immediate post induction heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse oximetry readings were noted. Then patient was turned to left lateral position for caudal block. Position was maintained by assistant. Caudal block was performed with 22 G hypodermic needle with loss of resistance to air technique. Patients were turned immediately supine after performing caudal block. Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were noted at caudal block and every fifteen minutes then till end of surgery (closure of surgical skin incision).

At the end of surgery anaesthetic agents were tapered and discontinued. After adequate recovery they were shifted to post operative care unit and monitoring of heart rate, mean arterial pressure, FLACC score, sedation score and pulse oximetry reading in immediate postoperative period and thereafter at first, second, third, fourth, sixth, nineth,12^{th},15^{th},18^{th},21^{th} and 24^{th} hours was done. A fall of mean arterial pressure of more than 30% from the baseline values during study period was con-

sidered as hypotension and this would have been treated with decreasing sevoflurane concentration, rapid infusion of fluids (ringer lactate 10 ml/kg) and intravenous ephedrine in aliquots of 0.02mg/kg. A fall in heart rate less than 80 beats per minute during study period was considered as bradycardia and this would have been treated with injection atropine 0.01 mg/kg. Caudal block was considered failed if heart rate was more than 30 % of baseline despite sevoflurane concentration of 2.5% (volume percentage) in nitrous oxide and oxygen after 15 minutes. We encountered two failed caudal block during study hence they were excluded. Respiratory depression was defined as decrease in intra-operative pulse oximetry reading to less than 93% or post-operative respiratory rate less than 12/min and this would have been treated with supplemental high concentrations of oxygen and if required assisted ventilation. Patient was also monitored for intraoperative and postoperative complications like bradycardia, hypotension, nausea, vomiting, respiratory depression etc. Duration of surgery was measured from making of skin incision to skin incision closure. 4 Point Sedation Score (PSS) was used to quantify post-operative sedation and is as follows, 1-Asleep, not arousable by verbal contact, 2-Asleep, arousable verbal contact, 3-Drowsy or not sleeping, 4-Alert or awake. Postoperative pain was assessed by anaesthetist using FLACC score (Table 1). FLACC score of more than four was consistent with diagnosis of pain and rescue analgesia (paracetamol 15mg/kg intravenously) was administered. Patients were excluded from study after administration of rescue analgesia. Duration of analgesia was defined as time between placement of caudal block and FLACC score of more than four.

Sample size calculation was based on clinically significant difference of 0.15 between two group means of Observer pain scale, with standard deviation of 0.20, obtained from pilot study with 95% confidence interval, 5% level of significance, using power of study 80%. A sample size of 28 patients per group was obtained.

	0	1	2
Face	No expression or smile	Occasional grimace or frown,withdrawn, uninterested	Frequent 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/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

Table 1. FLACC Scale

So we took 30 patients in each group. For continuous quantitative data, mean and standard deviations were used as a measure of central tendency. For qualitative data frequency and percentages were used.

Unpaired Student's *t* test was used to compare independent group.

A p value of <0.05 and <0.001 was considered significant and highly significant respectively. Sedation score among the two groups was analyzed by Mann-Whitney U test

Results

Statistical analysis was performed on 60 paediatric patients who were included in the study. Five children did not meet the inclusion criteria and two children did not experience successful caudal block, hence were excluded. There was statistically insignificant difference among the two groups as regards age, weight, ASA grading and duration of surgery. In our study all the p tients were male due to the type of surgeries chosen (Table 2).

Patient characteristics	Group L (n=30)	Group LD (n=30)	P value
Age (year)	5.63±3.057	5.27±3.172	0.656
Weight (kg)	14.63±3.970	14.2±4.46	0.694
Sex (M/F)	30/0	30/0	-
ASA grade (I/II)	28/2	27/3	0.64
Duration of surgery(min)	39.83±13.92	41.17±17.65	0.76

Table 2. Group comparison for demographic parameters

Comparison of mean heart rate among two groups showed statistically non-significant variation (P > 0.05) at the time of premedication, before induction, after induction, caudal block and at 15 minutes intraoperatively and significant variation (P < 0.05) at 30,45,60 and 75 minutes during intraoperative period and during post-operative period up to 6 hours.

Mean heart rate at ninth and twelth hour were 96.67 and 106.50 respectively in Group LD.

In group L, the fall in heart rate was never more than 30% from baseline value hence none of the patients required intervention (Table 3).

Comparison of mean arterial pressure among two groups showed statistically non-significant variation (P > 0.05) at the time of premedication, before induction, after induction and caudal block and significant variation (P < 0.05) at 15, 30, 45, 60 and 75 minutes during intraoperative period and during postoperative period up to 6 hours.

Mean arterial pressure at ninth and twelth hour were 73.27 and 76.85 respectively in Group LD.

The fall in mean arterial pressure was never more than 30% from baseline value hence none of the patients required intervention (Table 4).

Comparison of FLACC score among two groups showed statistically non-significant variation (P>0.05) at 1 h postoperatively and statistically highly significant variation at second, third, fourth and sixth hour postoperatively.

Time interval	Group L (n=30)	Group LD (n=30)	P value
Premedication	127.20±19.173	116.77±23.042	0.62(NS)
Before induction	127.63±15.889	120.57±20.631	0.143(NS)
After induction	126.60±16.724	124.93±20.502	0.73(NS)
Caudal block	127.33±16.074	125.03±21.067	0.63(NS)
Intraoperative at 15 min	117.00±18.482	112.03±19.051	0.31(NS)
Intraoperative at 30 min	107.41±17.860	97.37±15.205	0.024(S)
Intraoperative at 45 min	102.75±16.515	87.80±14.438	0.012(S)
Intraoperative at 60 min	103.86±16.618	87.60±16.087	0.00(S)
Intraoperative at 75 min	98	88.33±17.786	0.021(S)
Immediate post-operative	99.13±16.903	85.23±15.296	0.001(S)
Postoperative at 1 hour	98.57±18.887	83.97±15.194	0.02(S)
Postoperative at 2 hour	100.80±20.720	84.20±19.452	0.002(S)
Postoperative at 3 hour	103.67±15.722	92.13±16.286	0.007(S)
Postoperative at 4 hour	107.17±16.320	93.87±16.203	0.002(S)
Postoperative at 6 hour	105.82±14.299	98.37±19.062	0.099(S)
Postoperative at 9 hour		96.67±17.843	
Postoperative at 12 hour		106.50±17.352	

Table 3. Group comparison for mean heart rate (beats/min) during Intraoperative and Postoperative period.

There were not enough valid cases to perform Mann-Whitney test for immediate postoperative period, 9h and 12 h postoperatively (Table 5). Mean duration of analgesia in minutes in Group L and LD by using FLACC score is 440±53.240 and 769.66±86.859 respectively (p value <0.001). Duration of analgesia was prolonged (statistically highly significant) in group LD compared to group L. It indicates that administration of rescue analgesic was early in patients receiving levobupivacaine

alone. Comparison of 4 point sedation scale among two groups showed statistically significant variation ($p<0.05$) at immediate postoperative period,first,second and third hour postoperatively and statistically non-significant ($p>0.05$) variation at fourth and sixth hour postoperatively. There were not enough valid cases to perform Mann-Whitney test for nineth and 12th postoperatively (Table 6).

Time interval	Group L(n=30)	Group LD(n=30)	P value
Premedication	72.97±9.715	71.83±8.009	0.62(NS)
Before induction	72.57±9.369	72.70±8.334	0.954(NS)
After induction	69.83±8.844	70.97±8.385	0.61(NS)
Caudal block	70.47±10.375	67.47±8.525	0.22(NS)
Intraoperative at 15 min	67.87±8.689	62.17±7.358	0.008(S)
Intraoperative at 30 min	64.66±7.350	59.83±6.571	0.010(S)
Intraoperative at 45 min	64.44±4.604	60.00±6.347	0.03(S)
Intraoperative at 60 min	65.14±2.795	61.20±6.573	0.0038(S)
Intraoperative at 75 min	66	63.33±1.528	0.001(S)
Immediate post-operative	67.47±7.157	64.00±6.772	0.059(S)
Postoperative at 1 hour	69.87±8.398	65.80±6.127	0.036(S)
Postoperative at 2 hour	68.85±7.989	63.90±6.023	0.008
Postoperative at 3 hour	75.63±8.185	68.30±7.316	0.001(S)
Postoperative at 4 hour	77.47±8.709	71.53±6.415	0.004(S)
Postoperative at 6 hour	77.96±9.244	73.20±7.322	0.033(S)
Postoperative at 9 hour	-	73.27±6.617	-
Postoperative at 12 hour	-	76.85±7.006	-

Table 4. Group comparison for mean arterial pressure (mmHg) during Intraoperative and Postoperative period.

Time interval	Group L (n=30)	Group LD (n=30)	P value
Immediate postop-erative	-	-	-
Postoperative at 1 h	0.00	0.00	0.317(NS)
Postoperative at 2 h	4	3	0.000(S)
Postoperative at 3 h	1	0.00	0.000(S)
Postoperative at 4 h	2	1	0.000(S)
Postoperative at 6 h	3	1	0.000(S)
Postoperative at 9 h	-	3	-
Postoperative at 12 h	-	3	-

Table 5. Group comparison of median value of FLACC score used for assessment of postoperative analgesia.

Time interval	Group L (n=30)	Group LD (n=30)	P value
Immediate postopera-tive	2.5	1	0.000(S)
Postoperative at 1 h	4	3	0.000(S)
Postoperative at 2 h	4	3.5	0.043(S)
Postoperative at 3 h	4	4	0.040(S)
Postoperative at 4 h	4	4	0.557(NS)
Postoperative at 6 h	4	4	0.334(NS)
Postoperative at 9 h	-	4	-
Postoperative at 12 h	-	4	-

Table 6. Group comparison of median value of 4 point sedation score used for assessment of postoperative sedation.

Discussion

Levobupivacaine is as efficacious as bupivacaine, but with a superior pharmacokinetic profile. Clinically, its use is well-tolerated in paediatric regional anaesthesia.[3,7,8,9] Dexmedetomidine also has a favorable safety profile with haemodynamic stability, which are in concordance with the reports published by several other authors.[2,4,10]

In our study changes in mean heart rate and mean arterial pressure in two groups were statistically significant but of no clinical significance. Patel et al studied effects of clonidine and dexmedetomidine (1 µg/kg of each) as an adjuvant to bupivacaine during caudal block in ninety paediatric patients and revealed comparable heart rate and mean arterial pressure in both groups without any clinically significant bradycardia and hypotension.[11] Manohar et al reported marginal fall (statistically insignificant) in mean heart rate in sixty paediatric patients who received caudal ropivacaine or bupivacaine along with dexmedetomidine (1 µg/kg).[12] Danyal et al studied effects of levobupivacaine alone and combined with morphine and did not observe any hypotension or bradycardia in either group.[13]various other studies also mentions the safety of dexmedetomidine as an adjuvant to local anaesthetics in paediatric population [2,5,6,11,14,15]our results are comparable with them.

We kept uniform premedication in all children to avoid the confounding effects of the premedicant drug in assessment of postoperative analgesia. FLACC score was used for assessment of postoperative analgesia because it is easy to use and provides objective evaluation. Review of literature did not report study on effect of dexmedetomidine on the duration of analgesia of caudal levobupivacaine block in pediatric patients undergoing herniotomy, orchiopexy and circumcision. The main finding of our study was the addition of dexmedetomidine 1 µg/kg to 0.25% levobupivacaine administered caudally in pediatric patients resulted in significant prolongation of postoperative analgesia duration(12.8hours) when compared with 0.25% levobupivacaine alone (7.3 hours). Our results regarding duration of analgesia are in agreement with Patel et al and Fares et al who reported the significant prolongation of analgesia with mean duration of 8.38 hours and 19.2 hours in patients receiving caudal bupivacaine 0.25% and dexmedetomidine 1 µg/kg respectively.[6,11]Dexmedetomidine enhances the action of local anaesthetics by acting on peripheral α_{2A} receptors and prolongs the sensory blockade via vasoconstrictor effect on blood vessels which reduces its systemic uptake.[12] Use of different local anaesthetics, various methods to assess the pain and statistical analysis must have resulted in variable duration of analgesia in above studies. In our study mean duration of analgesia was 7.3 hours in group receiving 0.25% levobupivacaine alone and several other studies also supported our findings.[4, 16, 17]

We found higher FLACC scores at second, third, fourth and sixth hour in postoperative period in Group L as compared to Group LD which were statistically highly significant. Inspection of median values in group LD revealed increase in FLACC score from nineth hour postoperatively. This indicates that duration of analgesia was longer in Group LD with less requirement of rescue analgesic compared to Group L. Saleh et al reported higher pain score in group receiving levobupivacaine than group receiving levobupivacaine and nalbuphine at 4, 6 and 12 hpostoperatively.[4] Fares et al studied FLACC score in paediatric patients receiving caudal bupivacaine(B) and bupivacaine with dexmedetomidine(BD) in postoperative period for twenty four hours. He observed significant reduction in FLACC score in group BD at 2, 4, 6, and 12 hours compared to group B.At eighteenth and twenty-fourth hours there was no significant difference.[6]

We found low sedation scores at immediate postoperative period and at 1, 2 and 3 h postoperatively in group LD as compared to group L which were statistically significant. After three hours the median values of sedation scores in both the groups was same and statistically not significant. This indicates sedation in postoperative period was longer in duration in Group LD than group L. Though patients were deeply sedated in group LD (asleep and non arousable by verbal contact), none of them experienced fall in spo_2 or decrease in respiratory rate perioperatively. Patel et al observed higher sedation score (sedated but arousable) in paediatric patients receiving clonidine and dexmedetomidine as an adjuvant to bupivacaine. After four hours the mean sedation

scores in both the groups was almost same and statistically not significant.[11]Fares et al used Ramsey sedation scale for assessment of postoperative sedation and noticed significantly higher sedation scores in group, BD starting immediately after surgery and up to 4 hours postoperative than group B and from sixth hour up to twenty four hours both groups had almost same sedation score.[6] De Negri, Ivani, Visconti et al also noted higher sedation score in patients receiving dexmedetomidine and clonidine. Our results are comparable with them.[18]

In our study we did not observe any perioperative complications like bradycardia, hypotension, nausea, vomiting, respiratory depression etc.our results are comparable with other studies.[6, 11, 19]

Conclusion

We find dexmedetomidine (1 µg/kg dose) is haemodynamic safe and effective adjuvant to caudal levobupivacaine 0.25% in paediatric patients. It achieved significant prolonged postoperative analgesia. No episodes of clinically significant variations, respiratory depression and postoperative complications were observed during the study.

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