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Intrathecal bupivacaine versus bupivacaine and clonidine in pediatrics: a double-blind controlled study

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Abstract

Background: Spinal anesthesia is establishing a place in pediatric daycare anesthesia as a possible substitute for general anesthesia in children undergoing infraumbilical abdominal or lower extremity surgeries. Clonidine intensifies the effect of bupivacaine when given intrathecally as an adjuvant.

Methods and Objective of study: This is a prospective randomized double-blind study carried out in 60 ASA physical status 1 and 2 (3–13 years) pediatric patients scheduled for infraumbilical abdominal or lower extremity surgeries. Participants were randomly allocated to two groups. Group B received hyperbaric bupivacaine 0.5% alone (0.4 mg/kg for wt. 5–15 kg or 0.3 mg/kg for wt. > 15 kg), and group BC received hyperbaric bupivacaine 0.5% (0.4 mg/kg for wt. 5–15 kg or 0.3 mg/kg for wt. > 15 kg) and preservative-free clonidine (1 μg/kg), comprising 30 patients each. The primary outcome was the measurement of the time of onset of sensory block, the maximum level of sensory block, duration of sensory block, and duration of post-op analgesia.

Results: The mean onset of sensory block was 3.04 ± 1.5 min in group BC vs. 5.01 ± 0.30 in group B $p = 0.0001$. The mean onset of motor block was also earlier in group BC 3.81 ± 0.38 min vs. 6.47 ± 4.66 min in group B $p = 0.0028$. The mean duration of analgesia was 391.33 ± 33 min in group BC vs. 194.5 ± 28 min in group B with a *p*-value of 0.0001. None of the patients belonging to either group demonstrated a segmental level higher than T_5.

Conclusions: We infer that clonidine is a good adjuvant to bupivacaine in spinal anesthesia in pediatric patients as far as comfort is concerned. It decreases the time taken for onset, has a longer duration of postoperative analgesia, and has a better quality of sedation with no added side effects as compared to bupivacaine alone, in pediatric patients undergoing surgeries below T_8 dermatome.

Keywords: Analgesia, Bupivacaine, Clonidine, Pediatric, Infraumbilical surgery

Background

Ever since the beginning of our world, pain remains the major perturb of humanity. Since then, there has been an omnipresent desire to understand this "pain" and control it. The most exigent part and one of the borderlines of contemporary anesthesia is the management of pain in the pediatric age group. August Bier in 1899 published a preliminary report on pediatric spinal anesthesia after he executed cocaine intrathecally in an 11-year-old boy for ischium abscess drainage (Chiari and Eisenach 1998).

There was renewed interest in pediatric regional anesthesia (RA) considering that RA can be complimentary to general anesthesia (GA) after it was realized that children do perceive pain. It was only in 1984 spinal anesthesia re-established its popularity when spinal anesthesia was given to high-risk former preterm neonates, as a means of restricting the incidence of postoperative apnea and bradycardia (Abajian et al. 1984).

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In the previous three decennia, lower abdominal perineal urogenital and lower extremity surgeries have seen a significant increase in the use of spinal anesthesia in pediatric patients (Dalens 1989; Berkowitz and Green 1951). With only insignificant corporal modification, sensory block provides deep and good muscle relaxation counting rapid onset and uniform demonstration. It is highly endorsed for children (Gerber 2000) endangered for postoperative apnea after GA. In the pediatric patients who present with respiratory tract infections and are not nil by mouth before the operation, spinal anesthesia is distinctively advocated (Harnik et al. 1986). Adults experience more post-dural puncture headaches in contrast to children.

The short duration of action and complaints of postoperative pain, when spinal anesthesia wears off, usually counterbalance its advantages. So, the call for demand is to prolong the duration of postoperative analgesia by escalating and increasing the time span of the sensory block without repudiating its effect on motor block intensity.

Clonidine, α_2 adrenergic agonist when given intrathecally, produces antinociceptive effects without any neurotoxicity and is useful in the treatment of somatic pain as corroborated by many studies (Chiari and Eisenach 1998; Racle et al. 1987; Dobrydnjov and Samarutel 1999; Bonnet et al. 1990). By blocking the pain conduction of A-δ fibers and C fibers, intrathecal clonidine achieves a high drug concentration in the vicinity of α_2 adrenoreceptor in the spinal cord. In vitro, it increases the potassium conductance in isolated neurons and thus escalates the conduction block of local anesthetics. Pain, cold, temperature, and touch sensation are conducted by A-δ fibers which are myelinated afferent sensory nerve fibers. On the other hand, pain, warm temperature, and touch sensation are conducted by C fibers which are nonmyelinated postganglionic sympathetic fibers (Niemi 1994; Rochette et al. 2004; Kaabachi et al. 2007).

Clonidine in the dose of 1 μg/kg reduces the need for postoperative analgesic demand without significant aftermath with a noteworthy refinement in spinal anesthesia duration and quality as corroborated by many studies (Chiari and Eisenach 1998; Racle et al. 1987; Dobrydnjov and Samarutel 1999; Bonnet et al. 1990; Niemi 1994; Rochette et al. 2004; Kaabachi et al. 2007). Spinal clonidine does not produce pruritis and respiratory depression in contrast to other spinal opioids (Niemi 1994; Rochette et al. 2004; Kaabachi et al. 2007).

The primary measure of the study was to find out the effectiveness of 1 μg/kg clonidine added to hyperbaric bupivacaine on the onset, quality, and duration of analgesia. The secondary measure of the study was to compare the hemodynamic changes during the intraoperative and postoperative period and the side effects if any in pediatric patients undergoing lower abdominal surgeries.

Methods

This is a prospective double-blind, randomized controlled study conducted on 60 ASA physical status 1 and 2 pediatric patients of age group 3 to 13 years and weight 12 to 30 kgs of either gender who were posted for infraumbilical abdominal or lower extremity surgeries after getting approval from institutional ethical committee. The study was conducted from September 2019 to February 2022 in Ahmedabad, Gujarat, India.

Patients with known sensitivity to drugs, injection-site-specific skin infection, history of coagulopathy, congenital malformation altering the surface anatomy, imprecise sepsis, children with known epileptic disorders or uncontrolled seizures, children with a ventriculoperitoneal shunt, and children with an unchecked respiratory tract infection or a foreseen difficult airway with parental denial were all excluded from the study.

All the patients underwent thorough preanesthetic checkups (PAC), including history taking, general and physical examination, and routine investigations. On the PAC visit, each patient's baseline heart rate, blood pressure, and respiratory rate were recorded. The parents and the children (who could understand) were elucidated about the aimed procedure and VAS score. Their due consent was obtained after all the doubts were explicated and tackled.

After fulfilling the inclusion criterion, patients were allocated to group B or group BC on the basis of the computer-generated randomization prepared by the PSM (preventive and social medicine) department of our college.

Group B ($n = 30$) = hyperbaric bupivacaine (0.5% alone)

Group BC ($n = 30$) = hyperbaric bupivacaine (0.5% + 1 μg/kg clonidine)

Dose of hyperbaric bupivacaine (Moller and Covino 1988)

Children weighing less than 5 kg:0.5 mg/kg

Children weighing 5 to 15 kg:0.4 mg/kg

Children weighing more than 15 kg:0.3 mg/kg

Preoperatively, all the patients were kept nil by mouth (NBM) for 6 h for solid and 2 h for clear fluid. Topical local anesthetic cream EMLA (Dalens 2019; Pascucci et al. 1988) (eutectic mixture of a local anesthetic) was applied to the planned site of lumbar puncture and probable sites of vene puncture and thereafter an hour before the consonant technique occlusive dressing was done on the day of operation.

An optimum-sized cannula was used for establishing venous access, and an infusion of ringer lactate was started at the rate of 6 ml/kg. Baseline values of vital parameters: heart rate, SpO_2, and blood pressure (systolic + diastolic) were noted after attaching the standard monitors. All the patients were premedicated with inj. glycopyrrolate 0.04 mg/kg, inj. ondansetron 0.008 mg/kg, and inj. midazolam 0.02 mg/kg intravenously. All children except those who were cooperative and calm were given ketamine 0.5 mg/kg, oxygen, and sevoflurane for 3 min, only to make the patient immobile for lumbar puncture. Keeping an eye on the oxygen saturation, children were positioned in the lateral decubitus position.

Midline approach lumbar puncture was done in $L_4{-}_5$ or $L_3{-}_4$ interspace with a suitable spinal needle after assuring precise asepsis. Free flow of clear CSF authenticated the intrathecal position. The study drug was crammed in a 2 ml syringe according to the assigned group before a lumbar puncture was performed. To elude the tracking of the drug, the spinal needle was kept in position for up to 5 s after the injection of the study drug (Kokki and Tuovinen 1998; Blaise and Roy 1986; Giaufre 2000).

The pediatric patient was reverted back to a supine position. Three minutes after discontinuing sevoflurane, sensory block was noted. The patient was kept only on an oxygen ventimask with an eye for a facial scowl and a change in heart rate as a reaction to pinprick.

Vital parameters were recorded at an interval of 5 min for the first 15 min and subsequently every 15 min. A fluid bolus of up to 10 ml/kg was used to counter a reduction in blood pressure (systolic) of more than 20% from the baseline (Dalens 2019; Kokki et al. 1998). Cardiovascular changes due to spinal block are generally short lasting and respond to a bolus of intravenous fluid (10 ml/kg). Cardiovascular stability in infants undergoing SA is probably related to smaller venous capacitance in the lower limbs leading to less blood pooling and to the relative immaturity of the sympathetic nervous system resulting in less dependence on vasomotor tone to maintain blood pressure. However, an injection of ephedrine 5 mg (1 ml) diluted to 3 ml (under the guidance of our pediatric department) was kept ready in case the patient does not respond to the intravenous fluid bolus. But none of the patients actually required ephedrine. A reduction of heart rate to less than 100 beats per minute or more than 20% from baseline was planned to be countered with inj. atropine 0.02 mg/kg (Kokki et al. 1998; Block and Covino 1985). Patients who endured respiratory interruption of $\leq$ 15 s along with $\leq$ 90% SpO_2, and reduction in heart rate, were planned to be treated with 100% O_2. If any ECG changes were recorded which were evocative of bupivacaine toxicity, i.e., an increase in T-wave amplitude (Dalens 2019; Cote Ryan Todres 2001), it could be because of accidental intravascular injection. After 5 min of spinal anesthesia, if there was an incomplete sensory blockade, it was tagged as an unsuccessful spinal. It was then supplemented with GA and not included in the study. When the child was apprehensive and restless but had an adequate block, then mask ventilation with a nitrous oxide-oxygen mixture was done (Kokki et al. 1998; Block and Covino 1985; Kokki et al. 1992). Any occurrence of complications such as a high spinal block was planned to be recorded. Additionally, any intravascular injection was also documented. The time span of the surgery was recorded.

After the procedure concluded and before being transferred to the post-op ward, all the pediatric patients were carefully watched for 2 h in the recovery room. Every 5 min, the time for 2-segment regression was noted. Patients were observed postoperatively for analgesia using VAS scoring at 30, 60, 120, 180, 360, 400, and 480 min. When VAS was more than or equal to 5, then rescue analgesia in form of the paracetamol suppository was given, and its time of administration was noted. Postoperative complications such as vomiting, nausea, apnea, and headache were attended to if present.

Visual analogue scale

The scale consists of a 10 cm or 100 mm line anchored at one end by a label "no pain" and at the other end by a label "the worst pain imaginable." The patient simply marks the line to indicate pain intensity and a slide rule-like device with the line on the patient's side. VAS is the most common method for measuring pain and pain relief in clinical practice.

Sample size

The duration of analgesia was our primary outcome measure of interest. A previous study by Kaabachi et al. documented the mean (SD) for the duration of analgesia to be 330 (138) min in children undergoing surgery under spinal anesthesia. Assuming that the addition of clonidine will improve the duration of analgesia by 30%, with the permitted alpha error of 0.05 and beta error of 0.2 and the study power of 80%, a minimum sample size of 30 patients was required per group. Hence, we decided to recruit a total of 60 patients.

Randomization and blinding

Patients were randomized to one of the two groups using a computer-generated random number sequence maintained in sequentially numbered sealed opaque envelopes. Two anesthesiologists were involved in the study, and their roles are described below:

Table 1 Demographic variables mean SD

	Group B $n = 30$	Group BC $n = 30$	*p*-value
Age (yrs)	6.51 ± 2.06	6.06 ± 3.51	0.55
Sex (M:F)	28:2	28:2	
Weight (kg)	22.8 ± 5.70	22.3 ± 7.88	0.77
Height (cm)	120.33 ± 12.45	118.76 ± 17.46	0.69
BMI (kg/m^2)	15.58 ± 2.48	15.46 ± 2.26	0.84
ASA (I:II)	30:0	30:0	

$P \geq 0.5$ nonsignificant; ≤ 0.5 significant; ≤ 0.001 highly significant

- Anesthesiologist 1: Randomly allocates the patients to the study groups and loads the drugs for spinal.
- Anesthesiologist 2: Administers the intrathecal drug and monitors the VAS scale. They are blind to the choice of study drug injected to the patients.

Therefore, the patient, the person administering the intrathecal drug, and the outcome assessors were all blind to the group allocation.

Statistical analysis

At the end of the study, all data were compiled and analyzed statistically. Descriptive data were presented as mean and standard deviation, and continuous data were analyzed by paired/unpaired Student *t*-tests. A chi-squared test was used to assess the statistical difference between the two groups. It was considered significant when the *p*-value was less than 0.05 while employing the Student's *t*-test to collate the mean between both groups.

Results

There was no significant difference in both groups in terms of demographic variables. The mean age in years was 6.51 ± 2.06 in group B while 6.06 ± 3.51 in group BC with a *p*-value of 0.55, which was not significant. The mean weight in kilograms was 22.8 ± 5.70 in group B and 22.3 ± 7.88 in group BC with a *p*-value of 0.77, which was also not significant. Both groups had an equal sex ratio with the ratio being 28:2 (males: females). All patients were of ASA physical status 1 (Table 1). The types of surgeries in both groups were also comparable (Table 2).

There was an earlier onset of sensory block in group BC (3.04 ± 1.5) compared to group B (5.01 ± 0.30) with a *p*-value of 0.0001. Similarly, the onset of motor block was also earlier in group BC (3.81 ± 0.38 min) when compared with group B (6.47 ± 4.66 min.) with a *p*-value of 0.0028.

The mean duration of surgery was almost similar in both the groups which was 57.16 ± 22.21 min in group B and 59.33 ± 20.79 min in group BC, and the *p*-value was 0.69, which was nonsignificant.

There was smooth and prolonged analgesia for 391.33 ± 33 min in group BC as compared to group B where analgesia lasted for only 194.5 ± 28 min with a *p*-value of 0.0001, which is statistically significant (Table 3).

None of the patients belonging to either group demonstrated a segmental level higher than T_5. Children in group B demonstrated consistently higher levels of sensory blockade. Fourteen patients achieved T_6 in group B, and 14 patients achieved T_8 in group BC with a *p*-value of 0.0001 (Table 4).

Table 2 Type of surgeries

	Group B		Group BC	
	$n = 30$	%	$n = 30$	%
Herniotomy	18	60	22	73
Hydrocoele	3	10	0	00
Orchidopexy	1	3.33	1	3.33
Appendicectomy	2	6.66	2	6.66
Tibia nailing	4	13.33	1	3.33
Tibia nail ROI	1	3.33	0	00
Hydrocele + phimosis repair	0	00	1	3.33
Herniotomy + orchidopexy	0	00	2	6.66
Femur nail ROI	1	3.33	0	00
Femur shaft no.—plating	0	00	1	3.33
Total	**30**	**100**	**30**	**100**

Table 3 characteristics of spinal block

	Group B	Group BC	*p*-Value
Onset of sensory blockade (min)	5.01 ± 0.30	3.04 ± 0.15	0.0001
Onset of motor blockade (min)	6.47 ± 4.66	3.81 ± 0.38	0.0028
Duration of surgery (min)	57.16 ± 22.21	59.33 ± 20.79	0.69
Duration of analgesia (min)	194.5 ± 28.5	391.33 ± 33.37	0.0001

$P \geq 0.5$ nonsignificant; ≤ 0.5 significant; ≤ 0.001 highly significant

Table 4 Achieved segmental level

Level of blockade	Group B $N = 30$	Group BC $N = 30$
T_5	2 (6.66%)	0
T_6	14 (46.66%)	1 (3.33%)
T_7	10 (33.33%)	11 (36.66%)
T_8	4 (13.33%)	14 (46.66%)
T_9	0	4 (13.33%)

Table 5 Mean VAS score

Time (min)	Group B $n = 30$	Group BC $n = 30$	*p*-value
15	1	1	
30	1.73 ± 0.45	1.16 ± 0.37	0.0001
45	2.53 ± 0.57	2.16 ± 0.37	0.004
60	3.66 ± 0.54	2.13 ± 0.34	0.0001
120	4.7 ± 0.46	2.56 ± 0.50	0.0001
180	5	2.83 ± 0.37	0.0001
240		3.73 ± 4.30	
360		4.5 ± 0.50	
420		5	

$P \geq 0.5$ nonsignificant; ≤ 0.5 significant; ≤ 0.001 highly significant

Table 6 Mean Ramsay sedation score

Time, min	Group B $n = 30$	Group BC $n = 30$	*p*-value
15	3 ± 0	3.97 ± 0.18	0.0001
30	2 ± 0	3.3 ± 0.47	0.0001
45	1.77 ± 0.43	3.3 ± 0.47	0.0001
60	1.77 ± 0.43	3.3 ± 0.47	0.0001
120	1.77 ± 0.43	3 ± 0	0.0001
180	1.57 ± 0.50	3 ± 0	0.0001
240	1.57 ± 0.50	3 ± 0	0.0001
360		2.97 ± 0.18	
420		2 ± 0	

$P \geq 0.5$ nonsignificant; ≤ 0.5 significant; ≤ 0.001 highly significant

An intergroup comparison of the mean VAS score was done by applying an unpaired *t*-test. Statistically significant differences were found from 30 min onwards until the rescue analgesia was given. VAS scores were very low in group BC as compared to group B (Table 5).

Ramsay sedation scores in our study were significant from 15 min to 3 h after the subarachnoid block. It showed that group BC patients were significantly (*p*-value 0.0001) more sedated than group B, but none of the patients in either group required supplemental oxygen. SpO_2 was above 97% at all times (Table 6)

Intergroup comparison of heart rate was measured after administration of spinal anesthesia at baseline 5, 10, 15, 30, 45, 60, 75, 90, and 120 until 480 min at an interval of every 30 min. There was no significant difference in the heart rate between the two groups (Fig. 1). Clinically, though, 2 children in group BC developed significant bradycardia which responded to intravenous atropine of 0.02 mg/kg. Intergroup comparison of mean arterial pressure was done at various time intervals post subarachnoid block and showed no significant difference between the two groups. There were no significant postoperative complications among the two groups. Only one patient from group BC had bradycardia which was immediately treated with an injection of atropine. One patient in each group complained of nausea; the number is insignificant.

Discussion

SA is an approved, easy technique and dependable and appears to be a possible replacement for GA in pediatric patients. However, it still remains relatively misspent if compared to GA in children in most institutions. Pediatric spinal anesthesia has manifested as a cautious

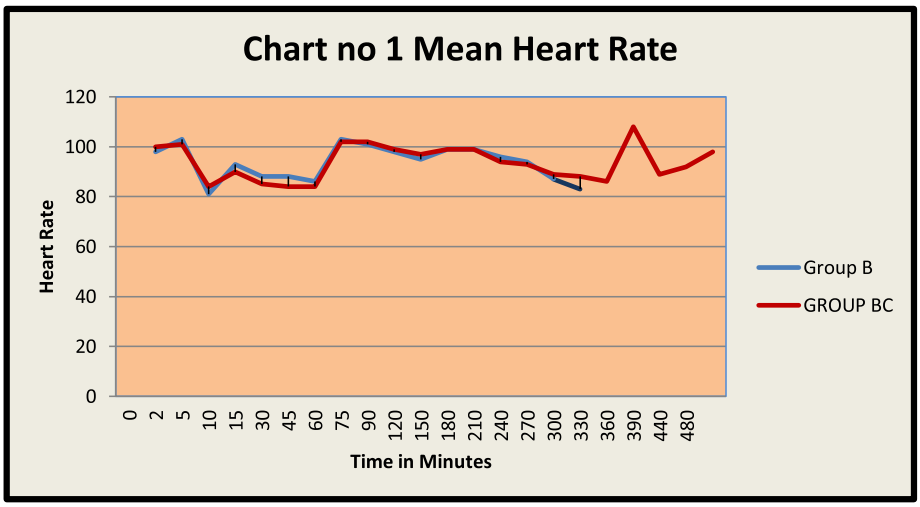

Fig. 1 Mean heart rate

substitute to conventionally administered general anesthesia as it avoids the polypharmacy associated with GA and also it prevents the incidence of postoperative respiratory complications.

SA is universally accepted in the clinical practice of anesthesia. Despite it producing excellent operating conditions with uniformly distributed analgesia and good neuromuscular blockade, its effect is short lived which is more in children than adults because of its efficient pharmacokinetics. Either potent systemic opioid analgesics are needed to extend the analgesia or intrathecal adjuvants are added to local anesthetics to prolong the analgesia. Systemic opioids are usually associated with a high incidence of respiratory depression, nausea, vomiting, itching, and urinary retention, so intrathecal adjuvants are preferred, devoid of such aftermath (Giaufre 2000; Kokki 1992).

Nickel et al. (2005) applied EMLA cream to the lumbar puncture area and IV cannulation site an hour prior to arrival in the operation room (not licensed for preterm < 37 weeks) and explained that good dermal analgesia might avoid the need for sedation in some children. In younger infants, ignorance acts as a prevention against panic, but older children require some premedication for easy parental separation, IV cannulation, and spinal puncture. Harnik et al. (1986) used midazolam, atropine, and ketamine alone or in combination by various routes (oral/rectal/IM) to provide sedation and anxiolysis. In our study, we applied EMLA cream at the site of IV cannulation and lumbar puncture an hour before the patient was taken to the operation theater irrespective of age.

Lopez et al. (2012) explained that during surgery under spinal anesthesia, it is important to soothe pediatric patients to prevent them from moving their bodies or bawling. Performing a spinal puncture in a struggling and agitated child might injure delicate neurovascular structures. SA by itself has sedative effects, probably due to a decrease in afferent input to the reticular activating system. Most children required additional sedation with ketamine, midazolam, thiopentone, propofol, halothane, sevoflurane, or nitrous oxide (Kokki et al. 2000a; Singh et al. 2010a; Ecoffey et al. 2010), while many infants were soothed with flavored pacifiers or sucrose-dipped dummy dip (Kokki 2012), before giving spinal blocks.

In our study, procedural sedation was given with ketamine 0.5 mg/kg BW IV with O_2 and sevoflurane for 3 min, whereas Singh et al. (2010a) used ketamine in a dose of 0.4 mg/kg BW with ketamine infusion vs. propofol induction and infusion. To counter the gestures and activities during surgery and anesthesia procedure, they used propofol 2 mg/kg BW as induction and an additional 1 mg/kg bolus; Brown et al. (2012) continued propofol in the dose of 25–50 μg/kg/min in contrast to 20–50 μg/kg/min by Puncuh et. al. (2004) in pediatric patients.

Gerber et al. (2000) studied spinal and caudal anesthesia in ex-premature babies. Harnik E. V. et al. (1986) studied spinal anesthesia in premature infants recovering from respiratory distress syndrome. Abajian et al. (1984) studied spinal anesthesia for surgery in high-risk infants, whereas Ze'evshenkman et al. (2002) studied 62 premature and former premature or young infants. In our study, we included the children in the ASA I and II physical status and were of 3–13 years, which was in correlation with Parag et al. (2019) who studied children aged 3–8 years, and Blaise et al. (Rice and Britton 1989) studied in 7 months–13 years, H. Kokki et al. (2007) in 10–15 years, and Jambure (2013) studied in 3–12 years, which was similar to our study.

Alan Rochette et al. (2004) studied spinal anesthesia with different doses of clonidine and concluded that 1 μg/kg of clonidine increased the duration of blocks twofold when compared with plain isobaric bupivacaine. This dose of clonidine was not associated with hemodynamic or respiratory alterations, whereas 2 μg/kg was associated with more side effects with the same duration of blockade. Bang et al. (Bang-vojdanovski 1996), Lindo et al. (Rice and Britton 1989), and E. Giaufre (2000) used clonidine in a dose of 1 μg/kg without any hemodynamic instability or high spinal. We had similar observations in our study. The reason could be that the large volume/kg BW of cerebrospinal fluid in children allows a greater volume of distribution in the intrathecal space. Hypotension is also prevented by the immaturity of the sympathetic nervous system in children.

In our study, we preloaded the patient with Ringer lactate at 10 ml/kg, and none of the patients had hypotension which is comparable with the studies of Blaise et al. (1986) and Kokki and Hendolin (2000) (Brown 2012) where they preloaded with crystalloid 5–10 ml/kg. On the contrary, N. Jambure (2013) and Junkin et al. (2011) did no preloading in their studies with no reported hypotension.

The addition of clonidine to bupivacaine as an adjuvant resulted in the early onset of sensory block 3.16 ± 1.4162 min compared to bupivacaine alone, 4.8 ± 1.54 in the study by Jambure (2013) and similar in (Kaabachi et al. 2007). All these block characteristics were statistically significant on the comparison ($p < 0.0000001$) which co-related with our study where there was earlier onset of sensory block in group BC (3.04 ± 1.5) when compared to group B (5.01 ± 0.30) with a p-value of 0.0001. Similarly, the onset of motor block was also earlier in group BC 3.81 ± 0.38 min when compared with group B 6.47 ± 4.66 min with a p-value of 0.0028.

Kokki and Hendolin (2000) achieved an average segmental level of blockade of T_4 with a lower dose and T_{5-6} with a higher dose. They used transcutaneous electrical

stimulation to check the level of the spinal blockade. In contrast, none of the patients in our study, belonging to either group, demonstrated a level higher than T_5. Children in group B demonstrated consistently higher levels of sensory blockade; 14 (46.66%) patients achieved T_6 in group B, whereas 14 (46.66%) patients achieved T_8 in group BC. The testing was done by the pinprick method.

Duration of analgesia was considered as the interval from the time of intrathecal injection to the time when analgesia was demanded postoperatively. The requirement for rescue analgesia is reduced by deep analgesia provided by intrathecal clonidine, which also extends the period until the sensory block's regression and the recuperation of the motor block (Filos et al. 1994). The duration of the block was 181 ± 59 min in the plain isobaric bupivacaine group as compared to 252 ± 79 min in the clonidine group in the study done by Kaabachi et al. (2007). Kumar Parag et al. (2019) (Kokki and Hendolin 2000) also reported profound analgesia with prolonged time to regression of the sensory block and recovery of motor block, with decreasing need of rescue analgesia as compared to intrathecal fentanyl which co-related with our study where group BC provided the smooth and prolonged analgesia of 391.33 ± 33 min as compared to group B where analgesia lasted for only 194.5 ± 28 min which was statistically significant with $p = 0.0001$.

In our study, statistically significant differences in VAS were found from 30 min onwards until the rescue analgesia was given. They were very low in group BC as compared to group B which is co-related with the studies done by N. Jambure (2013).

The results of the study done by Rochette et al. (2004), Batra et al. (2010b), and Cao et al. (2011) clearly marked the effectiveness of intrathecal clonidine as a subtle sedative. The patients showed a response on gentle excitation. Statistically, we see clonidine sedation scores were highly convincing. In all patients, SpO_2 was maintained at more than 90%. Mean sedation scores were also higher in group B than in group A (Cao et al. 2011; Singh et al. 2010b; De Sarro et al. 1987) and significant statistically i.e., ≤ 0.0000001. Ramsay sedation scores in our study were significant from 5 min to 3 h after the subarachnoid block. It showed group BC patients were more sedated than group B, but none of the patients in either group required supplemental oxygen, and SpO_2 was above 97% at all times.

Due to the sympathetic fiber block, cardiovascular changes, reduction in heart rate, and fall in blood pressure are common corporal reactions during spinal anesthesia. As cardiovascular stability in children is good (Dohi and Naito 1979), spinal anesthesia is well tolerated by infants with few general autonomic alterations. (Bang-vojdanovski 1996) Being a centrally acting drug, clonidine easily crosses the blood-brain barrier and stimulates the central alpha-2 receptors. This decreases norepinephrine release and reduces sympathetic outflow to the heart and vascular system, which causes bradycardia hypotension and reduces peripheral vascular resistance.

None of the patients had significant bradycardia as reported by H. Kokki (2007), G. A. Blaise (1986), and Junken et al. (1933) where the mean heart rate was less in group 1 as compared to group 2, reached statistical significance after 10–40 min of skin incision, which was quite similar to our study and which also showed no significant difference among the two groups.

Mean arterial pressure in our study showed no significant difference among the two groups, except at the 5-min time mark where the *p*-value is 0.001. This suggests that there was no statistically or clinically significant change in the mean arterial pressure. It correlated with the studies of Hannu Kokki (2007), N. Jambure (2013), Blaise et al. (1986), Junken et al. (1933), and Kumar et al (2019).

Kumar et al. (2019) reported bradycardia (heart rate dropped to 60) in 3 children in group 1 and none of the children in group 2, which was treated with atropine. N. Jamubure (2013) reported bradycardia in 2 patients in clonidine group 1 patient in bupivacaine alone which responded to intravenous atropine 0.02 mg/kg. In our study, only one patient (33.33%) in the BC group had bradycardia which was treated with intravenous atropine.

Kumar et al. (2019) found that when a propofol bolus was given in reaction to an intraoperative movement, there was the majority of desaturation incidences seen in group 2. Nevertheless, at no point was the SpO2 of any patient recorded lower than 90% and so were the complications such as apnea and respiratory obstruction which occurred post-propofol bolus administration, resulting in deep sedation. This underscores the significance of intraoperative respiratory monitoring and the provision of additional oxygen to every patient undergoing regional anaesthesia with sedation. None of the patients in our group had desaturation, and all the patients in either group maintained O_2 saturation equal to or more than 97%.

Kaabachi et al. (2007) reported hypotension was more frequent, 29% in the clonidine group and 17% in the control group, while hypotension incidence was 1–10% in adolescents with spinal anesthesia as reported by others (Kokki and Tuovinen 1998; Puncuh et al. 2004; Bangvojdanovski 1996; Kokki and Hendolin 2000). None of the patients in our group had hypotension which could be well related to preloading with ringer lactate 10 ml/kg.

PDPH was thought to be rare in children < 10 years of age, because of low CSF pressure, highly elastic dura, and non-ambulation. Lately, it was reported in children as young as 2 years, suggesting that its occurrence is independent of age (Nickel et al. 2005) Overall incidence

of 4–5% (as in adults) has been reported in 2–15 years age group (Kokki et al. 1998; Kokki et al. 2000b) Symptoms were mild. Studies reported a similar incidence of PDPH with pencil point and cutting needles (Hennaway et al. 2009) and a lesser incidence with pencil point (0.4% vs. 5%) (Junkin 1933). None of the patients in our study reported PDPH.

Conclusions

We conclude that clonidine is a good adjuvant to bupivacaine in spinal anesthesia in pediatric patients as far as comfort is concerned. It decreases the time taken for onset and produces a longer duration of both surgical anesthesia and postoperative analgesia and better quality of sedation with no added side effects as compared to bupivacaine alone, in pediatric patients undergoing infraumbilical surgeries.

Abbreviations

ASA: American Society of Anesthesiology; CNS: Central nervous system; CVS: Cardiovascular system; RS: Respiratory system; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; ECG: Electrocardiogram; F: Female; M: Male; GA: General anesthesia; RA: Regional anesthesia; HR: Heart rate; RR: Respiratory rate; Inj.: Injection; IV: Intravenous; kg: Kilogram; mm of Hg: Millimeter of mercury; min: Minutes; hrs: Hours; µg: Micrograms; mg: Milligrams; NBM: Nil By mouth; SD: Standard deviation; Wt.: Weight; Yrs.: Year; LA: Local anesthetic; NSAIDS: Nonsteroidal anti-inflammatory drugs; VAS: Visual analogue scale; PAC: Preanesthetic checkup; PONV: Postoperative nausea and vomiting; PACU: Postanesthetic care unit; CXR: Chest X-ray; Hb: Hemoglobin; TC: Total count; EMLA: Eutectic mixture of local anesthetic.

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Authors' contributions

UB and MP contributed to the conception and design of the study. Both organized the data collection, reviewed, and greatly contributed to the interpretation of results. SA, FBK, JG, and NP performed the laboratory analysis and collection of data. All authors have checked the statistical analysis and critically reviewed its comprehensive content and finally approved the version to be submitted for publication. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee of AMC MET Medical College and LG Hospital under registration number AMCMETIRB dated 21 July 2018. Informed oral consent was obtained from all participants (if they could understand as they all were under 13 years) and informed written consent from their parents or guardians. Consent of patients was verbal consent in front of witnesses (resident of anesthesia and relative of patients).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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References

Abajian JC, Mellish RW, Browne AF, Perkins FM, Lambert DH, Mazuzan JE Jr (1984) Spinal anesthesia for surgery in the high risk infant. Anesth Analg 63:359–362
Bang-vojdanovski B (1996) 10 years of spinal anesthesia in infants and children for orthopedic surgery. Our clinical experience. Anesthetist 45:271–277
Berkowitz S, Green BA (1951) Spinal anesthesia in children. Report based on 350 patients under 13yrs of age. Anesthesiology 12:376–386
Blaise GA, Roy WL (1986) Spinal anesthesia for minor pediatric surgery. Can Anesth Soc J 33(2):227–230
Block A, Covino BG (1985) Effect of local anesthetic agents on cardiac conduction and contractility. Reg Anestesial 6:55
Bonnet F, Buisson VB, Francois Y, Catoire P, Saada M (1990) Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth 15(4):211–214
Brown TCK (2012) History of pediatric regional anesthesia. Pediatric Anesthesia 22:3–9
Cao JP, Miao XY, Liu J, Shi XY (2011) An evaluation of intrathecal bupivacaine combined with intrathecal or intravenous clonidine in children undergoing orthopedic surgery. Pediatr Anesth 21:399–305
Chiari A, Eisenach JC (1998) Spinal anesthesia: mechanisms , agents , methods, and safety. Regional Anesth Pain Med 23(4):357–362
Cote C, Todres ID, Goudsouzian NG, Ryan JR (2001) A practice of anesthesiology in infants and children, 3rd edn. WB Saunders, p 636–669
Dalens B (1989) Regional anesthesia in children. Anesth Analg 68:654–672
Dalens BJ (2019) Regional anesthesia in children: Miller's textbook of anesthesiology, 7th edn. p 2519–237
De Sarro GB, Ascioti C, Froio F, Libri V, Nisticò G (1987) Evidence that locus coeruleus is the site where clonidine and drugs acting at alpha 1-and alpha 2-adrenoceptors affect sleep and arousal mechanisms. Br J Pharmacol 90(4):675–685
Dobrydnjov I, Samarutel J (1999) Enhancement of intrathecal lidocaine by addition of local and systemic clonidine. Acta Anesthesiol Scand 43(5):556–562
Dohi S, Naito H (1979) Takahashi TAge-related changes in blood pressure and duration of motor block. Anesthesiology 50:319–323
Ecoffey C, Lacroix F, Giaufré E, Orliaguet G, Courrèges P (2010) Epidemiology and morbidity of regional anesthesia in children: A follow-up one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists (ADARPEF). PediatrAnesth 20:1061–1069
Filos KS, Goudas LC, Patroni O, Polyzou V (1994) Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. Anesthesiology 81:591–601
Gerber AC (2000) Spinal and caudal anesthesia in ex-premature babies. Best Pract Res Clin Anesthesiol 14:673–685
Giaufre E (2000) Risks and complications of regional anesthesia in children: Bailliere's Clinical. Anesthesiology 14(4):650–671
Harnik EV, Hoy GR, Potolicchio S, Stewart DR, Siegelman RE (1986) Spinal anesthesia in premature infants recovering from respiratory distress syndrome. Anesthesiology 64:95–99
Hennaway AMEI, Abd- Elwahab AM, Abd-elmaksoud AM, Ozairy HSEL, Boulis SR (2009) Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anesth 103:268–274
Jambure N (2013) Intrathecal bupivacaine vs bupivacaine and clonidine in pediatric age group. A comparative evaluation. Int J Anesthesiol 31:1–7
Junkin CI (1933) Spinal anesthesia in children. Can Med Assoc J 28:51–53
Kaabachi O, Zaraghouni A, Ouezini R, Abdelaziz AB, Chattaouni O, Kokki H (2007) Clonidine 1µg/kg is a safe and effective adjuvant to plain bupivacaine in spinal anesthesa in adolescents. Anesthanalg 105(2):516–519
Kokki H (2012) Spinal blocks. Pediatr Anesth 22:56–64

Kokki H, Hendolin H (2000) Hyperbaric bupivacaine for spinal anaesthesia in 7-18 yr old children: comparison of bupivacaine 5 mg ml-1 in 0.9% and 8% glucose solutions. Br J Anaesth 84(1):59–62
Kokki H, Tuovinen K (1998) Hendolin H.: Spinal anesthesia for pediatric day-case surgery: a double-blind, randomised, parallel group, prospective comparison of isobaric and hyperbaric bupivacaine; British. J Anesthesia 81:502–506
Kokki H, Heikkinen M, Ahonen R (2000a) Recovery after pediatric day case herniotomy performed under spinal anesthesia. Pediatr Anesth 10:413–417
Kokki H, Heikkinen M, Turunen M, Vanamo K, Hendolin H (2000b) Needle design does not affect the success rate of spinal anestheisa or the incidence of post puncture complications in children. Acta Anesthesiol Scand 44:210–213
Kokki H, Hendolin H, Vainio J, Partanen J (1992) Comparison of spinal anesthesia and general anesthesia. Anesthetist 41(12):765–768
Kokki H, Hendolin K, Turunen M (1998) Post-dural puncture headache and transient neurologic symptoms in children after spinal anesthesia using cutting and pencil-point pediatric spinal needles. Acta Anesthesiol Scand 42(9):1076–1082
López T, Sánchez FJ, Garzón JC, Muriel C (2012) Spinal anesthesia in pediatric patients. Minerva Anestesiol 78:78–87
Moller RE, Covino BG (1988) Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesthesia Analgesia 67:107–114
Nickel US, Meyer RR, Brambrink AM (2005) Spinal anesthesia in an extremely low birth weight infant. Pediatr Anesth 15:58–62
Niemi L (1994) Effects of intrathecal clonidine on the duration of bupivacaine spinal anesthesia, hemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy. ActaAnesthesiol Scand 38(7):724–728
Parag K, Sharma M, Khandelwal H, Anand N, Govil N (2019) Intraoperative comparison and evaluation of intrathecal bupivacaine combined with clonidine versus fentanyl in children undergoing hernia repair or genital surgery: A prospective, randomized controlled trial. Anesth Essays Res 13:323–329
Pascucci RC et al (1988) Effect of spinal anesthesia on chest wall displacement in infants. Anesthesiology 69:A773
Puncuh F, Lampugnani E, Kokki H (2004) Use of spinal anesthesia in pediatric patients: a single center experience with 1132 cases. Pediatr Anesth 14:564–567
Racle JP, Benkhadra A, Poy JY, Gleizal B (1987) Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg 66(5):442–446
Rice LJ, Britton JT (1989) Spinal anaesthesia does not compromise ventilation or oxygenation in high-risk infants: Anaesthesiology 71:A1021
Rochette A, Raux O, Troncin R, Dadure C, CapdevilaX. (2004) Clonidine prolongs spinal anesthesia in newborns: a prospective dose-ranging study. Anesth Analg 98(1):56–59
Shenkman Z, Hoppenstein D, Litmanowitz I et al (2002) Spinal anesthesia in 62 premature, former-premature or young infants-technical aspects and pitfalls. Can J Anesth 49:262–269
Singh R, Batra YK, Bharti N, Panda NB (2010a) Comparison of propofol versus propofol-ketamine combination for sedation during spinal anesthesia in children: randomized clinical trial of efficacy and safety. Pediatr Anesth 20:439–444

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