Egyptian Journal of Anaesthesia 34 (2018) 129–134

HOSTED BY

Contents lists available at ScienceDirect

Egyptian Journal of Anaesthesia

journal homepage: www.elsevier.com/locate/egja

Research article

Comparative study between intravenous dexmedetomidine and clonidine as premedication in pediatric patients undergoing spinal anesthesia

Reena*, Amit Kumar

Department of Anaesthesiology, Heritage Institute of Medical Sciences, NH-2, Bhadwar, Varanasi 221311, India

ARTICLE INFO

Keywords:
Premedication
Dexmedetomidine
Clonidine
Pediatric anaesthesia

ABSTRACT

Title: Comparative study between intravenous dexmedetomidine and clonidine as premedication in pediatric patients undergoing spinal anesthesia.

Background: Many techniques and drug regimens, with partial or greater success, have been tried from time to time to eliminate the anxiety component and to prolong the postoperative analgesia during regional anesthesia. In pediatric patients, anxiety and lack of cooperativeness for the regional procedure is the major problem in providing spinal anaesthesia. Alpha2-adrenergic agonists have both analgesic and sedative properties, when used as an adjuvant to regional anesthesia. They eliminate the anxiety, provide conscious sedation, lower the level of agitation and improve patient satisfaction. We designed a prospective, randomized, double-blind study, to evaluate and compare the efficacy of intravenous dexmedetomidine with clonidine as a premedication drug during spinal anaesthesia using intrathecal bupivacaine.

Materials and methods: In this prospective, randomized, double-blind study, 60 pediatric patients 4–10 years of age of the American Society of Anesthesiologists status I, scheduled for uro-genital surgery under spinal anesthesia, were randomly allocated into two groups of 30 each. Group DE received dexmedetomidine 1 $\mu g\,kg^{-1}$ and group CL received clonidine 1 $\mu g\,kg^{-1}$ diluted in 20 ml of normal saline intravenously over 10 min, 40 min before subarachnoid anaesthesia with 0.5% hyperbaric bupivacaine. The patients were monitored every 5 min for 1st 20 min and then every 10 min interval vitals were noted. Acceptable sedation score, parental separation anxiety level and degree of mask acceptance were assessed. Highest level of sensory blockade, time of two segment regression and time of first request of analgesic were also noted. Data was analyzed using Fisher's exact test or Chi-square test and the value of $P < 0.05$ was considered statistically significant.

Results: Group DE and CL had comparable sedation score ($p > 0.05$). However, parental separation anxiety score and mask acceptance score, were better in DE than CL group ($p < 0.05$). There was no significant haemodynamic differences between the groups ($p > 0.05$). Duration of analgesia was also prolonged in DE group.

Conclusion: Dexmedetomidine is superior to clonidine as a premedication drug in pediatric patients undergoing spinal anesthesia.

1. Introduction

In pediatric patients, anxiety and lack of cooperativeness for the regional procedure is the major problem in providing spinal anaesthesia. The analgesia produced by α2-agonist is due to their action at spinal, supra-spinal, direct analgesic and/or vasoconstricting actions on blood vessels [1]. The locus ceruleus is the important central neural structures where these drugs act to produce sedation, anxiolysis and analgesia [2]. The prolongation of spinal anesthesia after intravenous administration of dexmedetomidine and clonidine can be explained by the supra-spinal effects of these drugs [3].

A number of studies have evaluated effects of intravenous α2-agonists in adult patients undergoing spinal anaesthesia [3–7]. Few studies have assessed the role of parenteral dexmedetomidine in children but till date we did not find any study comparing the role of intravenous α2-agonists in pediatric patients undergoing spinal blockade [8–10]. Aim of the study is to evaluate and compare the effect of intravenous dexmedetomidine and clonidine as a premedication drug during spinal anaesthesia using intrathecal bupivacaine in pediatric patients posted for uro-genital surgeries.

Peer review under responsibility of Egyptian Society of Anesthesiologists.
* Corresponding author.
E-mail address: reena216@gmail.com (Reena).

https://doi.org/10.1016/j.egja.2018.07.001
Received 16 April 2018; Received in revised form 20 June 2018; Accepted 16 July 2018
Available online 19 July 2018

2. Materials and methods

Approval from the institutional ethical committee was taken for the study. Informed written consents were also obtained from parents of the children who were included for the study. Inclusion criteria were children 4–10 years of age, ASA status I, and undergoing urogenital surgeries under spinal anaesthesia. Exclusion criteria were unwilling parents, children with upper respiratory infection, ASA > I, any mental or psychiatric illness and children with known allergy to study drugs. 60 patients were randomly allocated to two study groups based on computer generated numbers provided in sealed envelopes. In the pre-operative area children were monitored for NIBP, HR, ECG and SpO2 and baseline values were recorded. Topical EMLA™ gel was applied at the desired site, 45 min before intravenous cannulation and appropriately sized intravenous cannula were secured in place. The study drugs were prepared and administered in the pre-operative area by one anesthesiologist who was not involved in perioperative monitoring and data collection.

Group DE received dexmedetomidine 1.0 $\mu g\,kg^{-1}$ and group CL received clonidine 1.0 $\mu g\,kg^{-1}$ diluted in 20 ml of normal saline, given intravenously over 10 min, 40 min before subarachnoid anesthesia with 0.5% hyperbaric bupivacaine (i.e. 30 min after completion of infusion).

Sedation level was assessed using a four point sedation scale [11], first assessment done 5 min after the completion of infusion, then at 15 min interval till patient was taken inside the OT:

1. Agitated, crying, anxious
2. Awake but calm
3. Drowsy but responds to verbal commands or gentle stimulation
4. Asleep

Score ≥2 were considered satisfactory.

Anxiety in a child during parental separation was assessed using four point parental separation anxiety scale (PSAS) [12]:

5. Easy separation
6. Whimpers but is easily reassured, not clinging to parents
7. Cries and cannot or is difficult to be reassured, but not clinging to parents
8. Cries and clinging to parents

PSAS score of 1 or 2 was considered satisfactory, after 30 min from stopping the infusion. Child was separated from the parents even if PSAS score was > 2 after 30 min from the completion of infusion.

The subarachnoid block was given in left lateral position using 27 G Quinke's spinal needle at L4-L5 inter space. The volume of bupivacaine heavy 0.5% in milliliters (ml) was calculated on the basis of Partha's formula, which is age in years divided by 5 [13]. As spinal blockade requires optimum positioning and child's co-operation, all children were anaesthetized with inhalational induction using sevoflurane administered via mask to facilitate spinal blockade. The ease of mask acceptance was assessed just before spinal blockade using a four point Likert scale: MAS (mask acceptance scale) [14].

1. Excellent (unafraid, cooperative, and accepts mask easily)
2. Good (slight fear of mask, easily reassured)
3. Fair (moderate fear of mask, not calmed with reassurance)
4. Poor (terrified, crying, or combative).

A score of 1 or 2 was considered satisfactory.

Primary outcome was number of patients showing acceptable PSAS ≤2, 30 min after completion of infusion. Other parameters assessed were number of patients achieving sedation score ≥2, and mask acceptance score ≤2 before spinal anaesthesia. Secondary outcomes were time of onset of sensory block, highest sensory level, time for two-segment regression of sensory block, and time of first request of analgesic. These assessments were made by a senior anaesthetist, who was blinded to the nature of premedication the children received.

After spinal blockade children were positioned supine. The patients were monitored every 5 min for 1st 20 min and then every 10 min interval vitals were noted. Hypotension requiring resuscitation was defined as fall in MAP (mean arterial pressure) by more than 20% of the baseline value. It was managed with a bolus of RL @ 20 ml/kg, if no response was seen then inj. Ephedrine 0.1 mg/kg was used in intravenous bolus. Clinical bradycardia was defined as fall in heart rate by more than 20% from the baseline value associated with hypotension or signs of hypoperfusion, which was managed with Atropine 0.02 mg/kg IV; maximum single dose being 0.5 mg. Sensory level was assessed using sterile pin prick technique bilaterally, appearance of facial grimace suggested pain at the particular dermatome. Highest level of sensory block was noted. Motor blockade could not be assessed specially in younger children as after receiving sevoflurane via mask (though for short duration), they were not able to follow commands. If the child experienced pain during the surgical stimulus, it was classified as failed spinal block. The patient was given GA with intubation and was excluded from the study for further data analysis. After completion of surgery, time for two segment regression of sensory block was noted. Time for first request of analgesic was also noted.

2.1. Statistical analysis

Based on a previously done study, minimum required sample size was 25 patients in each group to detect 35% difference in satisfactory PSAS score between the two drugs (clonidine and dexmedetomidine) at 0.05 level of significance and to provide 80% power to the study.[15] PSAS ≤2 was used for calculation, 30 min after the completion of infusion. PASS 14 Power Analysis and Sample Size software was used for calculation of sample size. To account for dropouts, it was decided to take thirty patients in each group. All values are reported as mean ± standard deviation or percentage (number) of patients. Data analysis for numerical data was performed by unpaired Student's *t*-test. Data analysis for categorical data was performed by Fisher's exact test or Chi-square test to detect differences for the scores. The level of statistical significance was taken as $P < 0.05$. The data were analyzed using SPSS statistical software (SPSS version 17 (SPSS IL, Chicago, IL, USA).

3. Results

A total of 83 patients were enrolled for the study, out of which 23 patients were excluded as they did not meet the inclusion criteria. Fig. 1 shows the study design. Both groups were comparable in terms of age, weight, height and sex distribution ($p > 0.05$) (Table 1). Since we applied EMLA cream well in advance of putting the intravenous cannula, most of the children co-operated in its placement.

The sedation score was checked after 30 min of completion of infusion, and the desired score of ≥2 was achieved in 24 (80%) children of group CL and 27 (90%) children in group DE, the difference between the groups was not significant ($p > 0.05$). The acceptable PSAS score of 1 or 2 (after 30 min of completion of infusion) was achieved only in 17 (56.66%) children in group CL, which was significantly lesser than group DE where 28 (93.33%) children could be easily separated from the parents ($p = 0.001$) (Table 2).

Just before spinal blockade, face mask acceptance score of 1 or 2 was observed in 15 (50%) children in group CL, while in group DE, 25 (83.33%) children easily accepted the face mask ($p = 0.006$).

Time of onset of sensory block was less in CL group. Higher sensory level was achieved in DE group, however the difference was insignificant. Time for sensory regression of two dermatomes and time of first requirement of analgesic was significantly longer in DE group than the CL group ($p < 0.001$) (Table 3).

HR and MAP in the DE group was found to be lower than that of CL group and difference was statistically significant at 5 min, 10 min, 20 min and 30 min after spinal anesthesia (Figs. 2 and 3). However none of the patients developed clinical bradycardia or hypotension

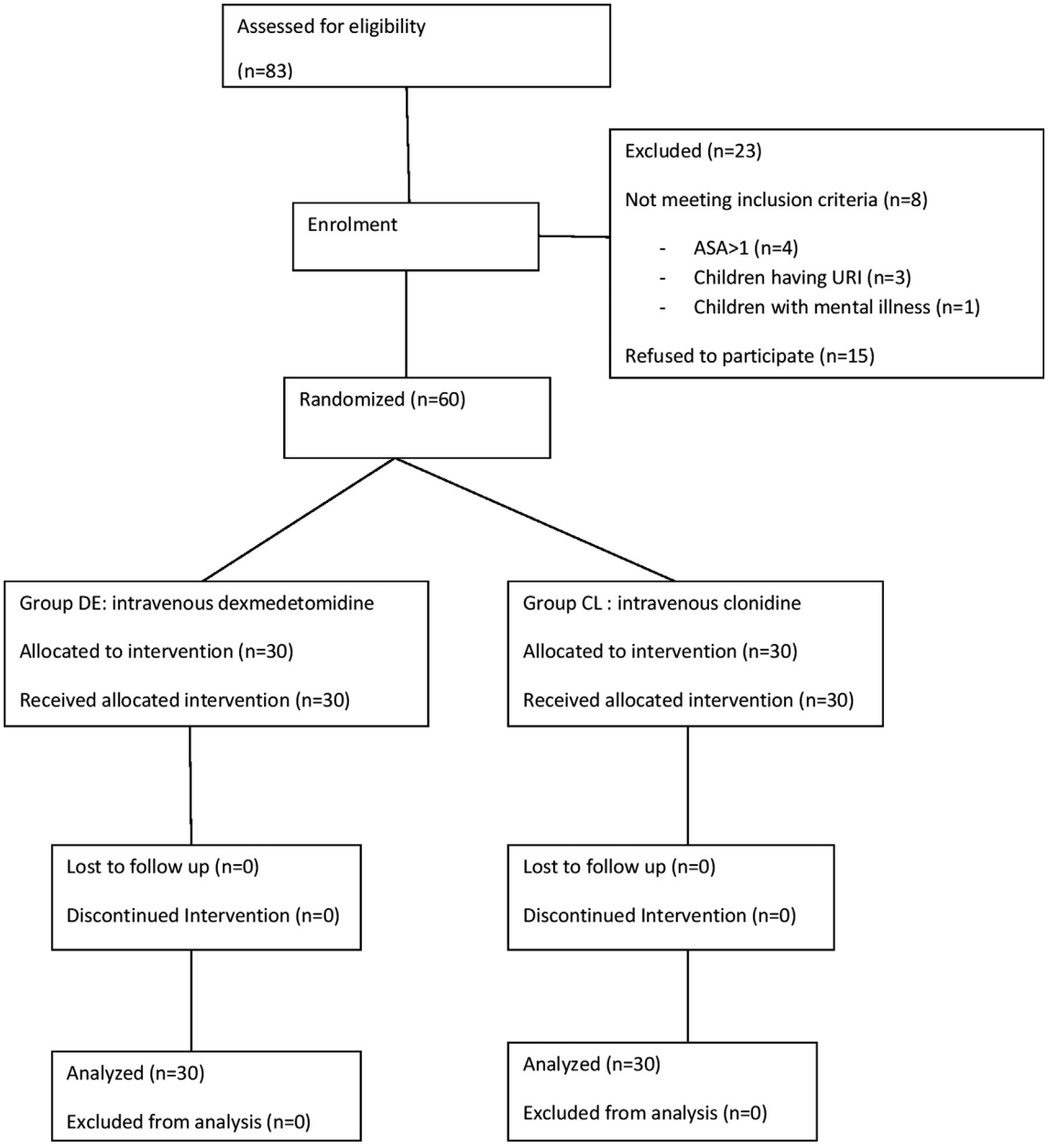

Fig. 1. Study design.

Table 1
Demographic profile.

	Group CL (n = 30)	Group DE (n = 30)	P-value
Age (years)	7.0 ± 3.0	7.5 ± 2.0	0.4506
Sex (M:F) (NUMBERS)	23:7	21:9	0.5593
Weight (kg)	19.0 ± 4.5	19.5 ± 5.0	0.6854
Height (cm)	45.0 ± 8.5	48.0 ± 6.5	0.1301

Values are expressed in Mean ± SD or in absolute numbers.

Table 2
PSAS, Sedation score, MAS.

No. of patients	Group CL (n = 30)	Group DE (n = 30)	p-Value
Sedation score ≥2 (after 30 min of infusion)	24	27	0.279
Parental separation anxiety score (PSAS ≤2) (30 min of completion of infusion)	17	28	**0.001**
Face mask acceptance score (MAS ≤ 2)	15	25	**0.006**

Values are expressed in absolute numbers.
* Bold values indicate $p < 0.05$ (statistically significant difference).

requiring resuscitation.

4. Discussion

In this study, we compared effects of single bolus infusion of dexmedetomidine and clonidine on children undergoing spinal anaesthesia for uro-genital surgeries. 28 patients receiving dexmedetomidine demonstrated PSAS ≤2 compared to only 17 patients receiving clonidine, 30 min after completion of infusion (93.33% vs 56.66%). Similarly, MAS ≤2 was found in 25 patients compared to 15 patients respectively. Dexmedetomidine has re- distribution half life of 6 min,

Table 3
Secondary outcomes.

	Group CL (n = 30)	Group DE (n = 30)	p-Value
Time of onset of sensory block (min)	3.85 ± 1.08	4.20 ± 1.20	0.2399
Highest sensory level (segments)	T5–T8	T4–T8	> 0.05
Time for two-segment regression of sensory block (min)	127.40 ± 17.06	149.66 ± 21.34	< **0.001**
Time of first request of analgesic (min)	192.65 ± 44.23	246.67 ± 53.22	< **0.001**

Values are expressed in Mean ± SD or level of blocks.
* Bold values indicate p < 0.05 (statistically significant difference).

for clonidine it is 20–30 min. So we had to allow at least 30 min time following the completion of both of the infusions as we were blind towards the exact composition.

Alpha-2 adrenergic agonists clonidine and dexmedetomidine, have a sedative effect produced by binding to post synaptic α2 receptors in Locus ceruleus and reducing the sympathetic outflow. Sleep produced by these agents resemble "normal sleep" as they predominantly affect the endogenous, non rapid eye movement sleep promoting pathways [16] contradictory to midazolam which by activating GABA receptors can cause clouding of consciousness and agitation on arousal [17]. Though not approved, use of dexmedetomidine in paediatric population as an off label drug has been described in literature for more than a decade specially in perioperative settings. In pediatric premedication, oral clonidine has been used in various studies due to its higher bioavailability (55.4%) [18], while oral dexmedetomidine has a poor bioavailability (16%) making oral route unsuitable for the later drug [19]. Introduction of topical analgesics (e.g EMLA™) has revolutionized the placement of IV lines, making IV premedication in children easy. So, we used intravenous route for an appropriate comparison between the two drugs.

Intravenous dexmedetomidine has been used in few studies for the purpose of pediatric sedation for radiological imaging [8–10,20]. Tammam et al. compared intramuscular and intravenous dexmedetomidine as pediatric premedications in children for MRI sedation [8]. They reported greater incidence of hypotension and bradycardia in intravenous group compared to intramuscular dexmedetomidine group, which can be attributed to use of maintenance infusion of dexmedetomidine at the rate of 1 μg/kg/h for the duration of the procedure. In children receiving subarachnoid blockade, de-afferentation itself produces sedation as proven by use of Bi-spectral index [21,22]. In children after spinal anaesthesia, a maintenance infusion might have resulted in greater degree of hypotension and bradycardia, requiring resuscitation. Instead, a single bolus over 10 min followed by spinal blockade maintained the haemodynamic stability in both the study groups besides supplementing sedation throughout the surgery. Due to paucity of literature on intravenous dexmedetomidine in children undergoing spinal blockade, it is difficult to make comparisons with any study which can corroborate with our findings.

In a comparative study between intranasal dexmedetomidine and midazolam, children in the dexmedetomidine showed better sedation scale 30 min after the premedication, resulting in easier parental separation and better mask acceptance [23]. In another study intranasal clonidine was compared to midazolam, better sedation and mask acceptance was seen in clonidine group [24]. Dexmedetomidine is a relatively selective alpha2-adrenergic agonist. It is chemically related to clonidine, but has a much greater affinity for alpha2-receptors over alpha1-receptors (1620:1 compared to 220:1 for clonidine) [25]. So, a better PSAS and MAS score in dexmedetomidine compared to clonidine group may be because of greater affinity of dexmedetomidine to alpha 2 receptor, more specifically to subtype 2A (which is mainly responsible for its anxiolytic and sedative effects) [16,26].

In our study, two-segment regression time of sensory block and time of first request for analgesic were significantly prolonged in the DE group than CL group. These findings are similar to observations by many other authors [4–7]. This could again be attributed to dexmedetomidine being eight to ten times more selective to α2-adrenoceptors especially for α2A and α2C subtypes compared to clonidine [2].

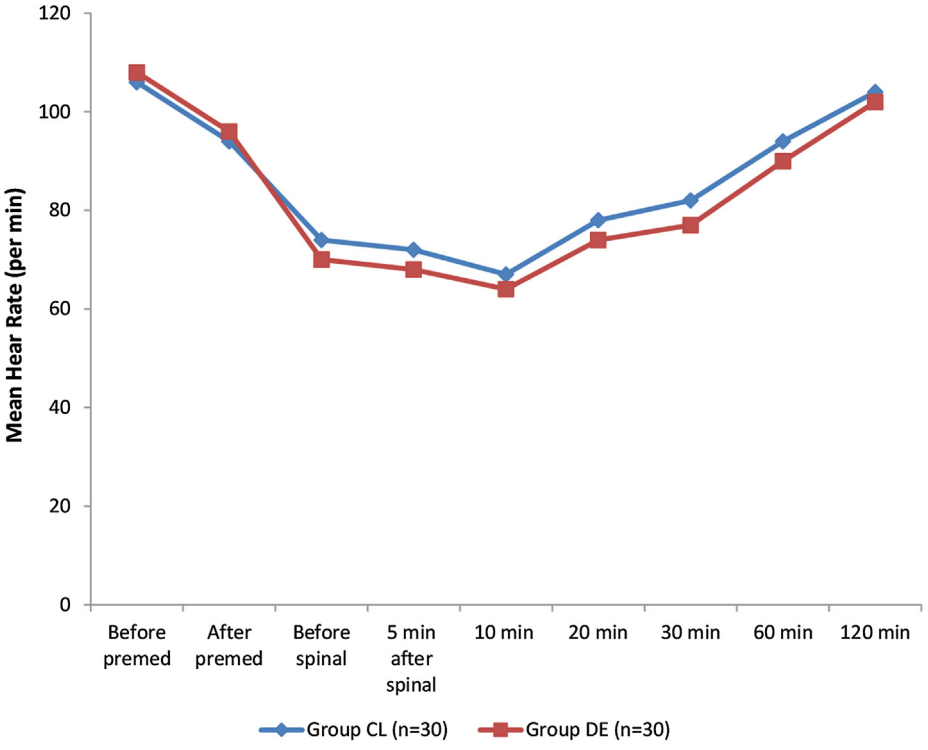

Fig. 2. Comparison of HR in the peri-operative period.

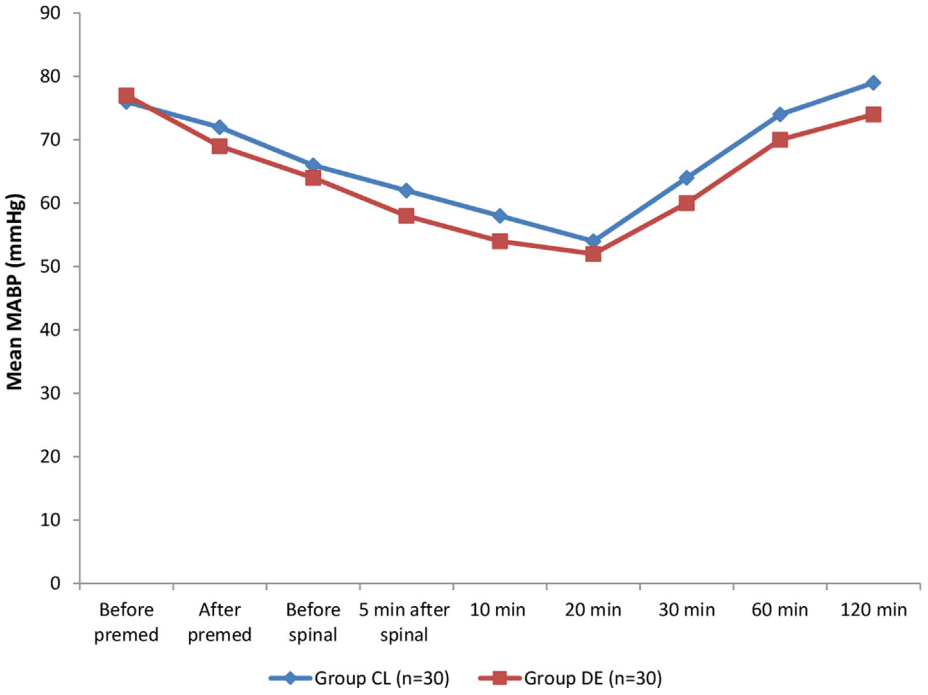

Fig. 3. Comparison of map peri-operatively.

Our study has some limitations too; first, dexmedetomidine has still not been approved for use in pediatric patients, but it is widely being used in children specially in peri-operative settings due to its innumerable benefits, which include hemodynamic stability, augmenting analgesia and anxiolysis and providing "wakeful sedation". A large centre randomized clinical trial is necessary to establish its efficacy and safety in children specially as an intravenous premedication. Also various doses of these drugs need to be titrated and compared to find out the most effective dose with minimum side effects profile with special consideration to hemodynamic alteration in pediatric patients undergoing spinal anaesthesia. We believe that since the drug is already being used in pediatric patients through various routes, using it intravenously under strict anaesthetic vigilance and haemodynamic monitoring can be considered for future studies, our study being one of the preliminary studies. Second, we did not include a placebo or control group, because placebos as premedication cannot be recommended in children as that will be a traumatic experience for them, and may cause behavioral problems in due course. Third, we chose intravenous route for premedication, which many physicians might consider inappropriate. However, topical anaesthetics have made painless iv cannulation possible and it is now no more a "forbidden" route in children. Also since the formulations of dexmedetomidine and clonidine easily available for anaesthetic use are for parenteral use only, using them in oral forms not only severely affects their bioavailability but can also interfere with the findings.

5. Conclusion

Single dose of intravenous dexmedetomidine resulted in, better parental satisfaction in the form of significantly higher number of children achieving the desired PSAS score; better face mask acceptance; increased time for two-segment regression of sensory block, prolonged duration of analgesia and stable cardiovascular parameters, thereby making intravenous dexmedetomidine an effective premedication drug than clonidine for children undergoing uro-genital surgeries under spinal anesthesia.

Conflict of interest

The authors declared that there is no conflict of interest.

References

[1] Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382–94.
[2] Feld JM, Hoffman WE, Stechert MM, Hoffman IW, Ananda RC. Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. J Clin Anesth 2006;18:24–8.
[3] Reddy VS, Shaik NA, Donthu B, Sannala VK, Jangam V. Intravenous dexmedetomidine versus clonidine for prolongation of bupivacaine spinal anesthesia and analgesia: a randomized double-blind study. J Anaesthesiol Clin Pharmacol 2013;29:342–7.
[4] Gupta K, Tiwari V, Gupta PK, Pandey MN, Agarwal S. Prolongation of subarachnoid block by intravenous dexmedetomidine for sub umbilical surgical procedures: a prospective control study. Anesth Essays Res 2014;8(2):175–8.
[5] Al-Mustafa MM, Badran IZ, Abu-Ali HM, Al-Barazangi BA, Massad IM, Al-Ghanem SM. Intravenous dexmedetomidine prolongs bupivacaine spinal analgesia. Middle East J Anesthesiol 2009;20(2):225–31.
[6] Harsoor S, Rani DD, Yalamuru B, Sudheesh K, Nethra S. Effect of supplementation of low dose intravenous dexmedetomidine on characteristics of spinal anaesthesia with hyperbaric bupivacaine. Indian J Anaesth 2013;57(3):265–9.
[7] Dinesh CN, Mohan CVR. Effects of intravenous dexmedetomidine on hyperbaric bupivacaine spinal anesthesia: a randomized study. Saudi J Anaesth 2014;8(2):202–9.
[8] Tammam TF, Wahba SS. Quality of MRI pediatric sedation: comparison between intramuscular and intravenous dexmedetomidine. Egypt J Anaesth 2013;29(1):47–52.
[9] Mason KP, Zgleszewski SE, Dearden JL, Dumont RS, Pirich MA, Stark CD, et al. Dexmedetomidine for pediatric sedation for computer tomography imaging studies. Anesth Analg 2006;103(1):57–62.
[10] Wong J, Steil GM, Curtis M, Papas A, Zurakowski D, Mason KP. Cardiovascular effect of dexmedetomidine sedation in children. Anesth Analg 2012;114(1):193–9.
[11] Jannu V, Mane RS, Dhorigol MG, Sanikop CS. A comparison of oral midazolam and oral dexmedetomidine as premedication in pediatric anesthesia. Saudi J Anaesth 2016;10:390–4.
[12] Dashiff CJ, Weaver M. Development and testing of a scale to measure separation anxiety of parents of adolescents. J Nurs Meas 2008;16:61–80.
[13] Parthasarathy S, Senthilkumar T. Age-based local anesthetic dosing in pediatric spinal anesthesia: evaluation of a new formula – a pilot study in Indian patients. Anesth Essays Res 2017;11:627–9.
[14] Mountain BW, Smithson L, Cramolini M, Wyatt TH, Newman M. Dexmedetomidine as a pediatric anesthetic premedication to reduce anxiety and to deter emergence delirium. AANA J 2011;79:219–24.
[15] Kumari S, Agrawal N, Usha G, Talwar V, Gupta P. Comparison of oral clonidine, oral

dexmedetomidine, and oral midazolam for premedication in pediatric patients undergoing elective surgery. Anesth Essays Res 2017;11:185–91.
[16] Hammer GB. The role of alpha2 agonists in pediatric anesthesia. Can J Anesth 2005;52(6):R1–3.
[17] Basker S, Singh G, Jacob R. Clonidine in paediatrics- a review. Ind J Anaesth 2009;53(3):270–80.
[18] Larsson P, Nordlinder A, Bergendahl HT, Lönnqvist PA, Eksborg S, Almenrader N, et al. Oral bioavailability of clonidine in children. Paediatr Anaesth 2011;21:335–40.
[19] Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. Br J Clin Pharmacol 2003;56:691–3.
[20] Mason KP. Challenges in paediatric procedural sedation: political, economic, and clinical aspects. Br J Anaesth 2014;113(S2):ii48-ii62.
[21] Gupta A, Saha U. Spinal anaesthesia in children: a review. J Anaesthesiol Clin Pharmacol 2014;30(1):10–8.
[22] Hermanns H, Stevens MF, Werdehausen R, Braun S, Lipfert P, Jetzek-Zader M. Sedation during spinal anaesthesia in infants. Br J Anaesth 2006;97:308–14.
[23] Singla D, Chaudhary G, Dureja J, Mangla M. Comparison of dexmedetomidine versus midazolam for intranasal premedication in children posted for elective surgery: a double-blind, randomised study. S Afr J Anaesth Anal 2015;21(6):154–7.
[24] Mitra S, Kazal S. Kanand L. Intranasal clonidine vs. midazolam as premedication in children: a randomized controlled trial. Indian Pediatr 2014;51:113–8.
[25] Grewal A. Dexmedetomidine: New avenues. J Anaesthesiol Clin Pharmacol 2011;27(3):297–302.
[26] Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. BUMC Proc 2001;14:13–21.