Comparative Study between Bupivacaine, Bupivacaine Plus Dexamethasone and Bupivacaine Plus Dexmedetomidine in Caudal Anesthesia for Pediatric Patients Undergoing Inguinoscrotal Surgery

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Abstract: Background: Caudal block is a popular and safe regional anesthesia method in pediatrics to provide intra and post-operative analgesia. Dexamethasone and dexmedetomidine may prolong caudal block with minimal side effects. **Aims:** The aim of the present study was to compare between the effects of bupivacaine, bupivacaine plus dexamethasone and bupivacaine plus dexmedetomidine in caudal block for pediatrics undergoing inguinoscrotal surgery. **Settings and Design:** double blinded randomized controlled study. **Methods:**105 patients, 1-6 y, ASA physical status classes I and II, < 25 kg, undergoing inguinoscrotal operations with duration > 100 minwere randomly divided into 3 equal groups (n=35) and received caudal block with 0.5 $mL.kg^{-1}$ bupivacaine 0.5%: Group I: no additives, Group II: bupivacaine plus dexamethasone (0.1 $mg.kg^{-1}$) and Group III: bupivacaine plus dexmedetomidine (1$\mu g.kg^{-1}$). **Results**: HR, MAP and BIS were comparable among the 3 groups. Postoperative modified objective pain scale was comparable till 3 hours, but it was significantly lower in dexamethasone and dexmedetomidine than control group at 4, 6 hours and lower in dexmedetomidine than dexamethasone group at 8, 10, 12, 16 hours. Time of 1st analgesia was delayed, and behavior score was significantly lower in dexmedetomidine than other two groups and in dexamethasone than control group. Sedation score showed a significant increase in dexmedetomidine compared to other groups, but no difference between dexamethasone and control group. Consumption of inhalation anesthesia was lower in dexmedetomidine than other groups to achieve the same level of BIS. **Conclusion:** Adding dexmedetomidine to caudal block prolongs postoperative analgesia with more sedation, less agitation and less inhalational anesthetic consumption compared to dexamethasone. Also, adding dexamethasone prolongs postoperative analgesia and decreases vomiting compared to bupivacaine alone.
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1. Introduction:

Caudal block is a popular and safe regional anesthesia method in pediatrics to provide intra and post-operative analgesia [1].

Bupivacaine is the usual local anesthetic but with a limited duration [2]. To overcome this problem, many additives have been used. Dexamethasone was added epidurally and showed prolonged block and avoidance of opioid usage and antiemetic effect in the postoperative period, however the exact mechanism is unclear[3].

Dexmedetomidine is a selective $\alpha_2$agonist which has 8 times affinity than clonidine. Initially it was used for sedation in intensive care, but now it extended for many uses (e.g. an adjuvant in regional anesthesia)[4]. It has many benefits as an anxiolytic, sympatholytic, sedative and analgesic drug[5].

The aim of the present study was to compare between the effects of bupivacaine, bupivacaine plus dexamethasone and bupivacaine plus dexmedetomidine in caudal block for pediatrics undergoing inguinoscrotal surgery.

2. Subjects and Methods:

After approval from institutional ethics and research committee (code number 30405/06/15), this double blinded randomized study was performed from September 2017 to August 2019 on 105 patients aged between 1 and 6years, ASA physical status classes I and II, weighing < 25 kg and undergoing inguinoscrotal operations like hypospadias repair with duration > 100 min. Full explanation of the procedure, possible side effects and complications were discussed. An informed written consent was obtained from the parents of the patient. There were adequate provisions to maintain privacy of participants and confidentiality of data like the patient had his secret code and private file and the photos applied only to the parts of body linked to the research and research results were only used for scientific purposes.

Exclusion criteria were: lack of parent consent, coagulopathy and other hemorrhagic diathesis, local (site of puncture) or untreated systemic infection, hypovolemia, spinal deformity and children with neurological disorders and allergy to bupivacaine or other local anesthetics.

Preoperatively, diet was allowed until 6 hours and clear fluids until 2-3 hours before induction. Two hours before surgery, EMLA cream was spread over to the dorsum of both hands. No pre-medication was given. After insertion of a 22-G cannula, maintenance fluid dextrose in normal saline6 $mL.kg^{-1}.h^{-1}$ was started.

The anesthetic technique was started with inhalation of sevoflurane in oxygen via the face mask till the patient become heavily sedated then a laryngeal mask airway of appropriate size was placed. In the operating theatre: peripheral oxygen saturation (SpO_2), ECG, non-invasive arterial blood pressure and bispectral index (BIS) were recorded until the end of surgery.

After induction of general anesthesia, a left lateral position with the upper hip flexed 90^O and the lower one 45^O was done. Under complete aseptic technique,[6,7]the needle was tilted 45–60° to skin to puncture of the sacral hiatus membrane, then the needle was minimally advanced, not more than 1–3 mm, in order to avoid a bloody puncture or an intrathecal injection.

Randomization of patient to the three groups was done by sealed opaque envelopes into 3 equal groups (35 patient in each) to receive caudal block with bupivacaine 0.5% (total volume $0.5mL.kg^{-1}$) **Group I** (bupivacaine group):no additive, **Group II** (dexamethasone group): bupivacaine plus dexamethasone 0.1 $mg.kg^{-1}$(1mL dexamethasone (4 mg) was diluted with 3 mL normal saline, so 1 mL of this solution had contained 1 mg) and **Group III** (dexmedetomidine group): bupivacaine plus dexmedetomidine (1 $\mu g.kg^{-1}$) (1 mL of dexmedetomidine (100 µg) was diluted with 9 mL of normal saline, so, 1 mL of this solution had contained 10 µg).

Measurements:

Heart rate (HR), Mean arterial blood pressure (MAP) and BIS was recorded before induction, after induction, after caudal anesthesia and then every 10 min for 30 min then every 15 min till the end of operation. HR and MAP were recorded from the end of surgery and for 24 hours postoperatively: Immediately after recovery, then every 30 min for two hours, then every two hours for 6 hours, then every four hours up to 24 hours post operatively.

Post-operative pain was assessed using an objective pain scale (OPS) [Table (1)]. Sedation level by using an objective score based on eye opening (spontaneously=0, in response to verbal stimulation=1 and in response to physical stimulation=2) [8], agitation: by using a behavior scale (a four-point scale: 1=calm; 2=not calm but could be easily calmed; 3=not easily calmed, moderately agitated or restless; and 4=combative, excited, or disoriented); Grades 1 and 2 indicated no agitation (= 0), while grade 3 (=1) and 4 (=2) indicated agitation[9]. All scores were recorded at 60-min intervals for four hours then only OPS and sedation scores were recorded at 6, 8, 10, 12, 16, 20, and 24 hours post-operatively.

Time of first analgesic dose after surgery (if OPS was ≥ 4 (inadequate analgesia), intravenous pethidine 0.5 $mg.kg^{-1}$ was given[10]) and complications of the procedure were recorded.

Outcome measures:

The primary outcome was time of first analgesic dose after surgery and the secondary outcome: OPS and consumption of inhalation anesthesia.

Statistical analysis:

Sample size calculation (N>30) was done by Minitab® 17.1.0 as time of first analgesic dose (the primary outcome) as the difference in mean was 7.8 with common SD 14.6 in a previous study[11], type I error (α) 0.05 and a power 99%. We added more cases to compensate for the dropped-out cases.

The statistical software was SPSS v25 (SPSS Inc., Chicago, IL, USA). Normality of data was checked with the Shapiro-Wilk test. Numerical parametric variables were presented as mean and SD. ANOVA or F-test was used for comparison among the three groups, post-hoc test (Tukey's test) was used to find which means are significantly different from one another and student paired T. test to compare between two means. Non-parametric variables (VAS) were presented as median and range and Kruskal Wallis test was used for comparison between three groups. Categorical variables were presented as patients' number and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. P value < 0.05 was considered significant.

3. Results:

In this study, 122 patients were assessed for eligibility, 11 patients did not meet the inclusion criteria and six patients' guardians refused to participate in the study. 105 patients were randomized into three groups (35 patients in each).

This study showed no significant difference among the three groups as regard age, gender, weight and duration of operation. As regard to HR and MAP, they were comparable between the three groups [Figure (1-4)].

Our study showed that postoperative modified OPS was comparable between the three groups till 3 hours postoperative, but it was significantly lower in dexamethasone and dexmedetomidine than control group at 4, 6hours postoperative and it was lower in

dexmedetomidine than dexamethasone group at 8, 10, 12, 16 hours postoperatively [Table (3)]. Therefore, the first analgesic dose was delayed in dexmedetomidine than other two groups and in dexamethasone group than control group [Table (6)].

As regards sedation score, we found a significant increase in the dexmedetomidine group compared to the other groups [Table (4)]. As regard to postoperative emergency agitation, it was significantly lower in dexmedetomidine than other groups [Table (5)].

As regard BIS, there was no significant difference between the three groups, but we observed that consumption of inhalation anesthesia in caudal dexmedetomidine was lower than other groups to achieve the same level of BIS [Figure (5, 6)].

As regard to postoperative side effects, our three groups were comparable according to urine retention and motor block, but vomiting is significantly lower in dexamethasone than the other groups [Table (2)].

Table (1): Objective pain scale (OPS)

Criteria	Finding	Point
Crying	None	0
	Consolable	1
	Not consolable	2
Movement	None	0
	Restless	1
	THashing	2
Agitation	Asleep	0
	Calm	0
	Mild	1
	Hysterical	2
Posture	Normal	0
	Flexed	1
	Holds injury site	2
Verbal	Asleep	0
	No complaint	0
	Complains but cannot localize	1
	Complains and can localize	2

Table (2): Comparison of the postoperative pain score among the three groups:

	Group I (n=35)	Group II (n=35)	Group III (n=35)	Kruskal Wallis test	P value	Post Hoc
1 H	0.74 ± 0.88 (0-3)	0.68 ± 0.86 (0-3)	0.45 ± 0.65 (0-2)	182	0.40	----
2 H	0.91± 0.81 (0-2)	0.80 ±0.83 (0-3)	0.60± 0.83 (0-2)	2.65	0.26	----
3 H	0.60 ± 1.84 (0-2)	0.85 ±0.80 (0-3)	0.69± 0.60 (0-2)	2.16	0.33	----
4 H	3.31 ± 2.16 (0-8)	0.88± 0.71 (0-2)	0.48 ± 0.65 (0-2)	48.34	<0.001	P1 <0.001 P2 <0.001 P3 0.053
6 H	4.37 ±1.40 (2-7)	0.94 ±0.68 (0-3)	0.68 ± 0.64 (0-2)	70.56	<0.001	P1 <0.01 P2 <0.001 P3 = 0.14
8 H	4.68 ± 1.98 (0-7)	3.34 ± 2.27 (0-8)	0.65 ± 0.68 (0-2)	51.15	<0.001	P1 0.03 P2 <0.001 P3 <0.001
10 H	3.25 ± 1.93 (0-7)	3.05 ± 1.21 (0-7)	0.62± 0.68 (0-3)	55.64	<0.001	P1 0.93 P2 0.001 P3 <0.001
12 H	3.37 ± 1.68 (0-7)	3.00 ±1.11 (0-5)	0.62 ± 0.64 (0-2)	57.84	<0.001	P1 0.62 P2 <0.001 P3 <0.001
16 H	3.31 ± 1.79 (0-7)	3.20 ± 1.69 (0-6)	2.08 ±1.57 (1-7)	5.63	0.005	P1 = 0.77 P2 = 0.003 P3 = 0.007
20 H	2.51 ± 2.18 (0-9)	2.97 ± 1.79 (0-6)	2.26 ± 1.39 (0-6)	3.07	0.21	-----
24 H	2.25 ± 1.26 (0-6)	2.11 ± 1.51 (0-7)	2.32 ± 1.64 (0-7)	0.32	0.83	-----

P1 group I vs group II. **P2** group I vs group III. **P3** group II vs group III

Table (3): Comparison of the sedation score among the three groups:

Sedation score	Group I (n=35)	Group II (n=35)	Group III (n=35)	Test of sig	P value	Post Hoc
1 H	0.74 ± 0.61 (0-2)	0.62 ± 0.64 (0-1)	1.51 ± 0.61 (0-2)	F=20.92	<0.001	P1 0.44 P2 <0.001 P3 <0.001
2 H	0.82 ± 0.70 (0-2)	0.85 ± 0.64 (0-2)	1.45 ± 0.61 (0-2)	F=10.23	<0.001	P1 0.85 P2 0.001 P3 <0.001
3 H	0.70± 0.62 (0-2)	0.74 ± 0.78 (0-2)	1.14 ± 0.64 (0-2)	F=4.29	0.01	P1 0.82 P2 0.01 P3 0.01
4 H	0.48 ± 0.70 (0-2)	0.48 ± 0.50 (0-1)	1.2 ± 0.66 (0-2)	F=31.43	<0.001	P1 = 1.00 P2 = 0.004 P3 = 0.01
6 H	0.57 ± 0.65 (0-2)	0.51 ± 0.50 (0-1)	1.11 ± 0.75 (0-2)	F=25.68	<0.001	P1 = 0.96 P2 = 0.006 P3 = 0.001
8 H	0.91 ± 0.61 (0-2)	0.85 ± 0.42 (0-2)	1.22 ± 1.05 (0-3)	K=2.28	0.31	----
10 H	0.94 ± 0.59 (0-2)	0.77 ± 0.42 (0-1)	1.11 ± 1.02 (0-3)	K=1.74	0.41	------
12 H	1.00 ± 0.68 (0-2)	0.85 ± 0.64 (0-2)	1.17 ± 0.85 (0-2)	K=3.20	0.20	------
16 H	0.54 ± 0.56 (0-2)	0.62 ± 0.49 (0-1)	0.65 ± 0.53 (0-2)	F=0.43	0.64	------
20 H	0.11 ± 0.32 (0-1)	0.28 ± 0.57 (0-2)	0.25 ± 0.44 (0-1)	K=2.50	0.28	-----
24 H	0.17 ± 0.38 (0-1)	0.28 ± 0.45 (0-1)	0.14 ± 0.35 (0-1)	K=2.47	0.29	------

P1 group I vs group II. **P2** group I vs group III. **P3** group II vs group III

Table (4): Comparison of the behavior score among the three groups:

Behavior score	Group I (n=35)	Group II (n=35)	Group III (n=35)	Kruskal Wallis test	P value	Post Hoc
1 H	3.05± 0.90 (1-4)	2.77±0.91 (1-4)	1.57±1.03 (1-4)	F= 23.95	<0.001	P1 0.21 P2 <0.001 P3 <0.001
2 H	2.60±01.03 (1-4)	2.25 ±0.70 (1-4)	1.17±0.61 (1-4)	K=46.34	<0.001	P1 0.29 P2 <0.001 P3 <0.001
3 H	2.28±0.92 (1-4)	1.97±0.74 (1-4)	1.08±0.50 (1-3)	K=39.61	<0.001	P1 0.32 P2 <0.001 P3 0.01
4 H	2.11±1.13 (1-4)	2.02±0.74 (1-4)	1.05±0.48 (0-2)	K=31.06	<0.001	P1 0.97 P2 <0.001 P3 0.01

P1 group I vs group II. **P2** group I vs group III. **P3** group II vs group III

Table (5): Comparison of mean time of 1st analgesia among the three groups:

	Group I (n=35)	Group II (n=35)	Group III (n=35)	Kruskal Wallis test	P value	Post Hoc
Time to 1st analgesia (hour)	4.65±1.37	8.34±1.57	16.68±4.28	89.67	<0.001	P1 <0.001 P2 <0.001 P3 <0.001

P1 group I vs group II. **P2** group I vs group III. **P3** group II vs group III

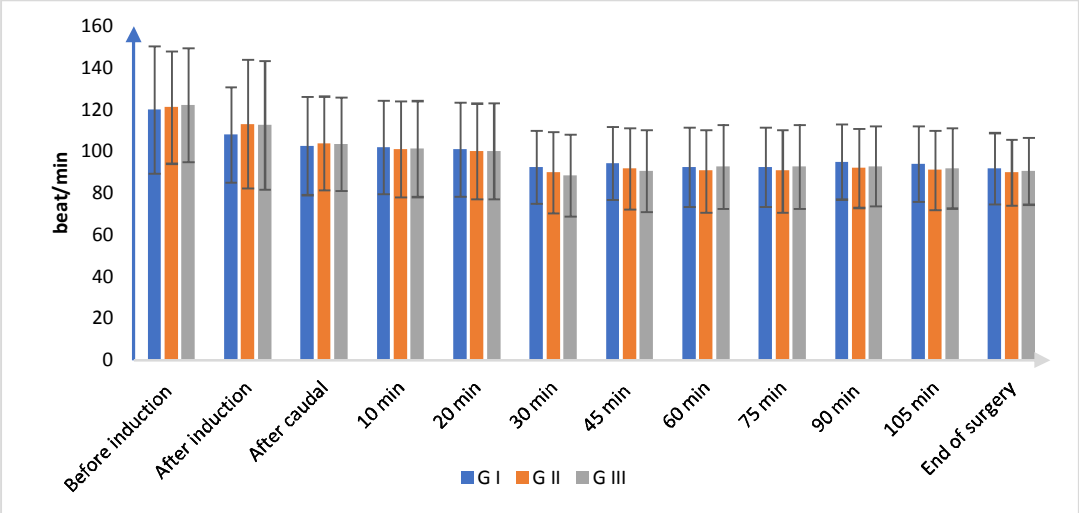

Figure (1): Comparison of the pre and intraoperative HR among the three groups

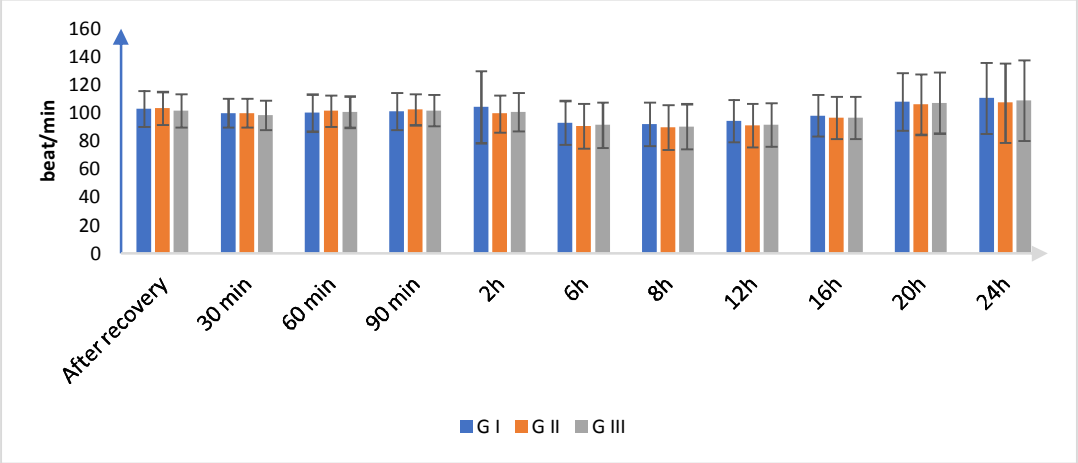

Figure (2): Comparison the postoperative HR among the three groups

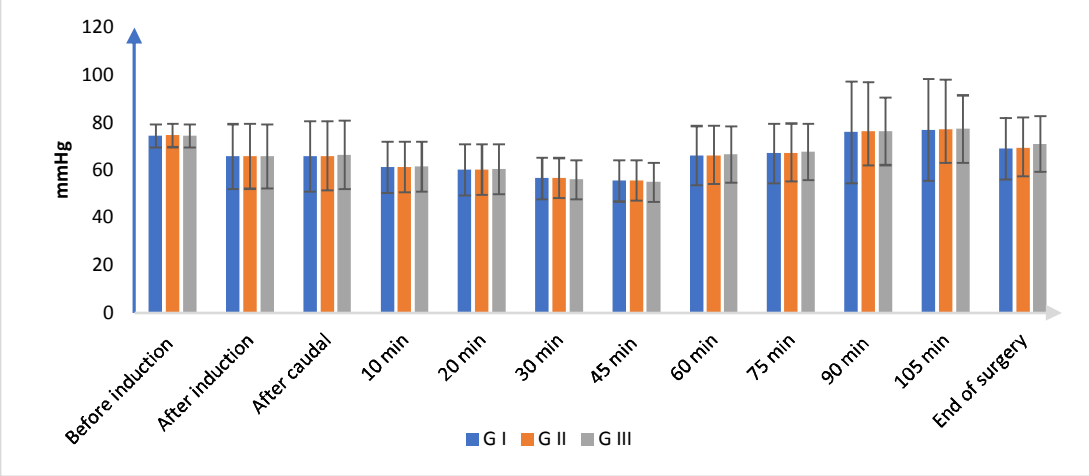

Figure (3): Comparison of the pre and intraoperative MAP among the three groups

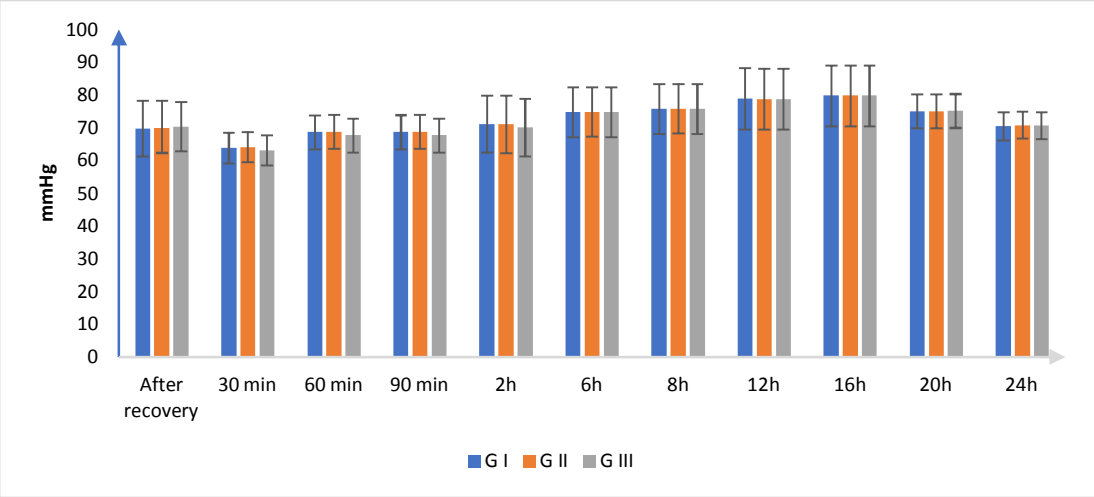

Figure (4): Comparison of the postoperative MAP among the three groups

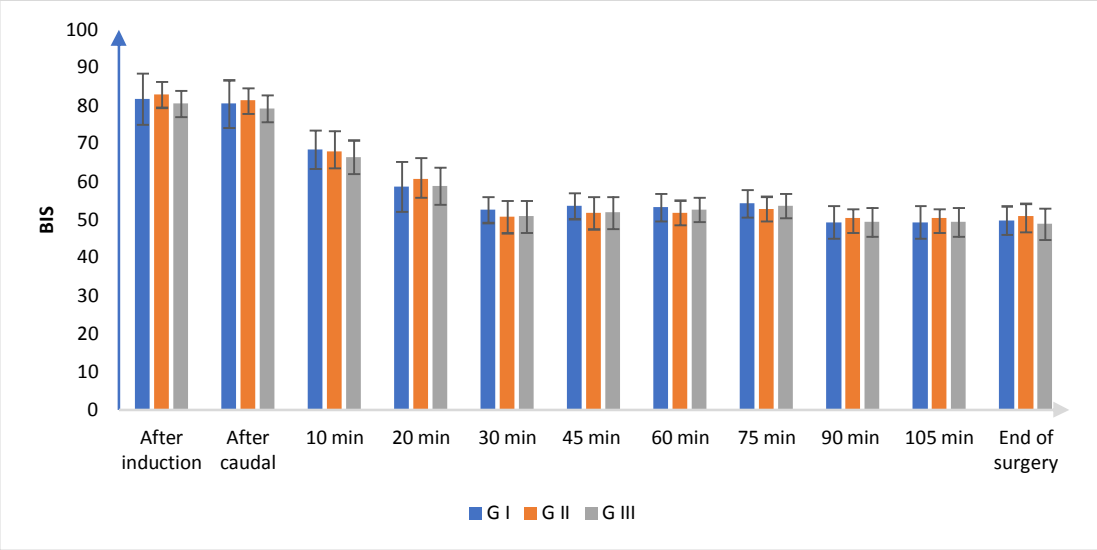

Figure (5): Comparison of BIS among the three groups

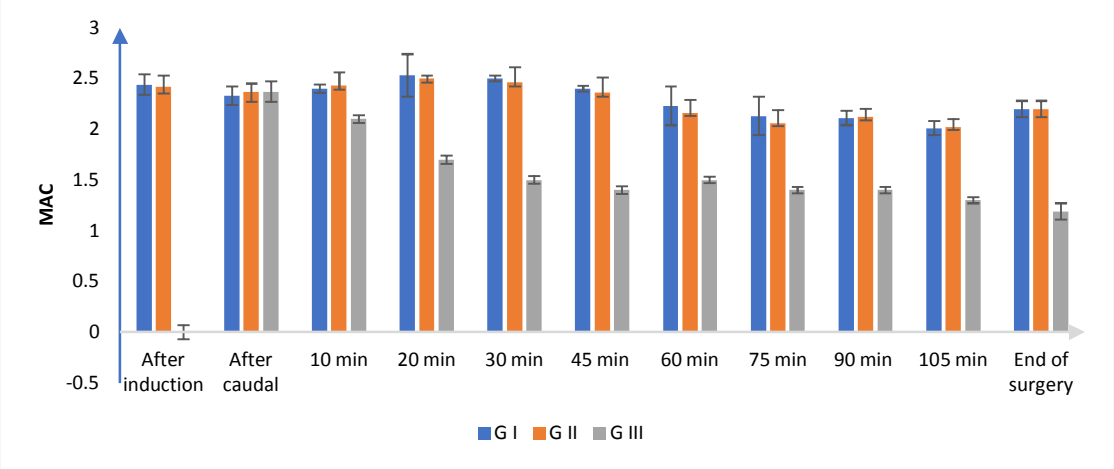

Figure (6): Comparison of MAC of sevoflurane among the three groups

4. Discussion:

Dexmedetomidine extends the duration of analgesia by many mechanisms: local vasoconstriction, increasing potassium conductance in A delta and C fibers, entering the central nervous system either via systemic absorption or by diffusion into the cerebrospinal fluid and reach α-2 receptors in the superficial laminae of the spinal cord and brainstem or indirectly activating spinal cholinergic neurons[12].

Also, Dexamethasone extends the duration of analgesia by possible mechanisms: its local anesthetic action (as a corticosteroid) and inhibiting nuclear factor-kB (NF-kB); which expressed in the nervous system and causes pain[13].

As regards HR and MAP, they were comparable between the three groups of our study. These results are in agreement with El Shamaa et al [14], Jarineshin et al[15] and Kannojia et al [16]who found that dexmedetomidine added to caudal bupivacaine had stable hemodynamics. Against our results, Nasr et al [17] who concluded that HR and MAP were significantly decreased with caudal dexmedetomidine.

In coordination with our results in postoperative modified OPS and first analgesic dose, Goyal et al [18] who found that children with a mixture of bupivacaine with dexmedetomidine has shown to improve the duration of caudal block with less number of rescue analgesics as compared to plain bupivacaine alone. The study done by El Shamaa et al [14] showed that dexmedetomidine added to caudal bupivacaine had longer postoperative analgesia when compared with morphine. Also, Al-Zaben et al [19] who concluded that caudal dexmedetomidine added to bupivacaine provided prolonged and greater postoperative analgesia compared to IV administration. Moreover. Parameswari, et al[20] concluded that dexamethasone added to caudal bupivacaine effectively improves the analgesic efficacy. Also, She et al[8] concluded that the addition of caudal dexmedetomidine reduced the minimum local anesthetic concentration of levobupivacaine and improved postoperative analgesia.

On the other side, Anand et al [21] documented that caudal dexmedetomidine in a dose of (2 $\mu g \cdot kg^{-1}$) with 0.25% ropivacaine (1mL.kg^{-1}) for pediatric patient achieved significant postoperative pain relief with its benefits when using larger dose of dexmedetomidine than the dose used in our study. Also, Girgis K[22] said that, they recommended that the addition of dexamethasone 0.2 mg.kg^{-1} to bupivacaine significantly prolonged the caudal block with lower postoperative pain scores and analgesic requirements. They also recommended the use of a larger dose of dexamethasone than that used in our study.

As regards sedation score, we found a significant increase in dexmedetomidine compared to the other groups, but insignificant difference between dexamethasone and control group.

Our results are supported by Saadawy et al. [23]who concluded that caudal dexmedetomidine had better quality of sleep and a prolonged duration of sedation. Also, Bong CL et al[24] concluded that dexmedetomidine sedation with caudal anesthesia is a feasible alternative to spinal or general anesthesia. Moreover, Kannojia et al[16] concluded that adding dexmedetomidine (1 $\mu g \cdot kg^{-1}$) to bupivacaine in caudal block provides arousable sedation in pediatric patients.

Against our results Sridhar et al [25] who said that the adjuvants to caudal anesthesia such as (dexmedetomidine, dexamethasone, and magnesium) added to ropivacaine prolong analgesic duration without any sedation or side effect. Also, El-Feky et al [11]found that the sedation score with caudal dexamethasone is lower than bupivacaine alone it but in the level, which is acceptable to the parents as there was no crying.

As regard to postoperative emergency agitation, we found that no significant difference in behavior score between dexamethasone group and control group but was significantly lower in dexmedetomidine than other two groups.

In coordination with our results, Mohamed et al[26]showed that the incidence and severity of agitation and pain scores were significantly lower in caudal dexmedetomidine compared to lidocaine alone. On the other side, Bharti et al[27] who studied4 groups: Group 1 received 0.2% plain ropivacaine 0.75 mL.kg^{-1}, while group 2, 3, and 4 received dexmedetomidine 0.5, 1.0, and 1.5 μg.kg^{-1}, respectively, along with 0.2% ropivacaine 0.75 $mL \cdot kg^{-1}$ and concluded that postoperative analgesia was significantly prolonged in all dexmedetomidine groups as compared to plain ropivacaine group. Patients receiving dexmedetomidine 1.5 $\mu g \cdot kg^{-1}$ were more sedated as compared to the other groups, but it did not delay discharge of the patients.

As regard to postoperative side effects, our three groups were comparable according to urine retention and motor block, but vomiting is significantly lower in patients received dexamethasone than the other two groups.

In agreement with our results, Al-Zaben et al [19]who concluded that caudal dexmedetomidine had no significant side effects. Also, Bajwa et al. [28] revealed that the incidence of postoperative nausea and vomiting (PONV) was significantly lower in dexmedetomidine group than the fentanyl group in epidural analgesia in lower limb surgeries. Moreover, Girgis et al [22] concluded that the adding

dexamethasone to caudal bupivacaine decreases the incidence of PONV. Also, Parameswari, et al[20] said that addition of dexamethasone to bupivacaine effectively had no significant side effects. Against our results El-Feky et al [11] who documented that PONV was comparable in those who received caudal dexamethasone, dexmedetomidine and who received no additive.

As regard BIS, there was no significant difference between the three groups, but we observed the consumption of inhalation anesthesia in caudal dexmedetomidine was lower than the other two groups to achieve the same level of BIS.

In agreement with our observation, Kang et al[29]said that dexmedetomidine reduced the propofol requirement for remifentanil-based anesthesia while producing more stable intraoperative hemodynamics. Also, Gozalo -Marcilla et at[30] demonstrated that co-administration of dexmedetomidine and morphine significantly reduced the MAC of sevoflurane compared with morphine alone.

4. Conclusion:

Adding dexmedetomidine to caudal block prolongs postoperative analgesia with more sedation, less agitation and less inhalational anesthetic consumption compared to dexamethasone. Also, adding dexamethasone prolongs postoperative analgesia and decreases vomiting compared to bupivacaine alone.

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Conflict of Interest: Nil

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