ORIGINAL RESEARCH   **PEDIATRIC ANESTHESIA**

A randomized controlled trial of dexmedetomidine vs magnesium sulfate as adjuvants to bupivacaine in infraorbital nerve block for perioperative analgesia in pediatric patients undergoing cleft lip surgery

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ABSTRACT

Background & Objective: Cleft lip surgery is routinely performed in children under general anesthesia (GA). Infraorbital nerve block (IONB) has been used by some anesthetists to enhance the perioperative pain management in addition to the routine intravenous analgesics. We compared the addition of dexmedetomidine (Dex) plus bupivacaine with magnesium sulphate (MgSO$_4$) plus bupivacaine for IONB in combination with GA, regarding their efficacy, effect on the duration of postoperative analgesia, and any adverse events.

Methodology: A total of 75 patients, aged 3 months to 7 y, of either sex, were randomly allocated into three equal groups. After induction of GA with a standardized method, Group D received IONB with Dex + bupivacaine; Group M received the nerve block with MgSO$_4$ + bupivacaine, and a control group (Group C) received block with bupivacaine only. Acetaminophen infusion was used when additional analgesic was required in the postop period. The primary outcome was the duration of time until the first analgesic was administered, while the secondary outcomes were the amount of acetaminophen taken within the first 24 h following surgery, pain scores, and the frequency of side effects.

Results: The mean time to first requested analgesia was significantly longer in the Group D, followed by the Group M, and it was the shortest in the Group C (13.9 ± 1.7 h, 11.5 ± 2 h, 5.9 ± 1.3 h respectively, P < 0.001). Total acetaminophen consumption and pain scores were significantly lower among the Group D than the Group M and highest in the Group C (P < 0.001). Emergence agitation and vomiting were non-significantly less frequent in the Group D than the Group M and more frequent in the Group C. No significant difference regarding hypotension, bradycardia, and shivering, was observed among all the groups. Respiratory depression was not recorded in any of the groups.

Conclusion: Dexmedetomidine and magnesium sulphate, both offered prolonged analgesia when added to bupivacaine for infraorbital nerve block for perioperative analgesia in pediatric patients undergoing cleft lip surgery under general anesthesia. However, dexmedetomidine was superior to magnesium sulphate regarding the duration of postoperative analgesia.

Abbreviations: ASA-PS - American Society of Anesthesiologists Physical Status classification; Dex – Dexmedetomidine; FiO$_2$ - Fraction of inspired oxygen; IONB - Infraorbital nerve block; MBP - Mean blood pressure; NIBP - Non-invasive blood pressure; PACU - Post Anesthesia Care Unit

Key words Bupivacaine; Cleft Lip; Dexmedetomidine; Infraorbital Nerve Block; Magnesium Sulfate

1. INTRODUCTION

Cleft lip is a congenital craniofacial birth anomaly with a high prevalence. It is described as an upper lip fissure that was present at birth. It may be unilateral, bilateral, complete (extending to the nasal cavity), or incomplete. It may also be accompanied by a palatal cleft.[1]

The most widely used anesthetic method for cleft lip repair is general anesthesia (GA) combined with infraorbital nerve block (IONB). Combined use of GA and IONB reduces intraoperative anesthetic requirements, postoperative pain, and total opioid use.[2] IONBs have been claimed to be effective for cleft lip repair;[3] however, the duration and effectiveness of the regional block following a single local anesthetic dose are limited. Hence, adjuvants have to be added to local anesthetics to potentiate and prolong the local analgesic effect.[4]

Compared to clonidine, Dex is a more selective α2-adrenoreceptor agonist. It also has more analgesic and opioid-sparing effects.[5] As an adjuvant to local anesthetics in peripheral nerve blocks, Dex has been recently introduced.[6] Perineural Dex has been demonstrated to decrease opioid consumption while also extending the duration of the postoperative sensory block.[7]

The analgesic effect of $MgSO_4$ has recently been recognized.[8] When combined with local anesthetics, $MgSO_4$ acts as an N-methyl-D-aspartate (NMDA) receptor antagonist and has been shown to decrease acute postoperative pain, analgesic consumption, or both.[9,10] In pediatric patients, $MgSO_4$ may be effective as an analgesic adjuvant in locoregional anesthesia.[11]

Moreover, adding $MgSO_4$ as an adjuvant to regional blocks improves and extends the analgesic effect of local anesthetics, speeds up recovery from surgery, and reduces the likelihood of emergence agitation.[12,13]

We aimed to compare the effectiveness of IONB using a combination of bupivacaine with Dex or $MgSO_4$ for perioperative analgesia as well as anesthesia-related adverse effects in pediatric patients scheduled for cleft lip repair.

2. METHODOLOGY

Formal approval of this study was obtained from the research ethics committee of the Faculty of Medicine, Ain-Shams University (No. FMASU R 176/2022), and it was registered at clinical trials.gov with ID NCT05624151 on November 21, 2022.

This prospective, randomized, controlled trial was carried out at the orthodontics and dentofacial surgery unit of Ain-Shams University hospitals. Patient enrollment was started on November 25, 2022, and ended on May 2, 2023. All patients' guardians provided their written, informed consent. The Declaration of Helsinki's guiding principles were followed in conducting the study.

A total of 75 pediatric patients of both sexes, 3 months to 7 y old, with an ASA-PS I or II, scheduled for elective cleft lip repair (cheiloplasty) under GA, were enrolled.

Patients with local infection at the injection site, generalized sepsis, coagulopathy, thrombocytopenia, hemophilia, complex congenital heart disease, renal failure, major illnesses, allergy, or contraindications to the study medication, and parental or guardian's dissent were excluded from the study.

During the preoperative visit, all patients underwent medical evaluation, focusing on the heart, lungs, and airways to identify any associated conditions or abnormalities. Routine laboratory investigations, e.g., a chest X-ray, complete blood count, and coagulation profile, were performed.

Instructions were passed to abstain from clear fluids like water and non-particulate juices for two hours, breast milk for four hours, formula or solid food for six hours, and fat-containing meals for eight hours.

Before induction of anesthesia, standard monitors were attached in the operating room, and basal readings for the patient's heart rate (HR), mean blood pressure (MBP), and oxygen saturation (SpO_2) were recorded.

Conventional GA was administered to every child. Patients were randomly assigned into one of the three groups (25 in each group) using computer-generated randomization numbers with a closed-seal envelope.

The first group (Group D) received bilateral IONB before surgical incision with one ml of a mixture of bupivacaine 0.25% plus 0.5 μg/kg Dex, while patients in the 2nd group (Group M) received bilateral IONB with one ml of a mixture of bupivacaine 0.25% with 2 mg/kg $MgSO_4$ to a maximum of 50 mg. Patients in the 3rd group (Group C) served as control, and received bilateral IONB with one ml of bupivacaine 0.25%.

Sevoflurane in an O_2/air mixture (FiO_2 = 0.8) with a sealed face mask was used to induce anesthesia in spontaneously breathing patients. A peripheral venous cannula was inserted after the patients' consciousness was lost. Fentanyl 1–2 µg/kg and propofol 1–2 mg/kg were administered to achieve a deep plane of anesthesia. Rocuronium 0.9 mg/kg was administered intravenously to facilitate endotracheal intubation with a preformed Ring–Adair–Elwyn (RAE) endotracheal tube, which was fixed centrally over the lower lip. Capnography confirmed the correct placement of the tube.

After fixing the endotracheal tube, pressure-controlled ventilation was adjusted to maintain normocapnia by continuously monitoring end-tidal CO_2 for adequate ventilation. According to age and body weight, Ringer's solution was infused in all patients. Sevoflurane in O_2/air mixture (FiO_2 = 0.3) at 1% minimum alveolar concentration and rocuronium supplementation at 0.15 mg/kg were used to maintain anesthesia.

The technique of IONB

Bilateral IONB was performed on all participants using the intraoral approach before surgical repair. The upper lip was pulled back after the infraorbital foramen was palpated, and a 28 G needle was then advanced to the foramen parallel to the maxillary premolar.

The needle was advanced cephalad by positioning a finger at the level of the infraorbital foramen. After negative aspiration on each side, the target volume was injected (Figure 1).

Figure 1: Infraorbital nerve block, intraoral approach

A pediatric anesthesiologist with five years of experience in pediatric regional nerve blockade performed IONBs.

Cardiovascular monitoring (HR, MBP) was maintained throughout the procedure; readings were taken every 5 minutes and recorded at specific intervals (baseline, after intubation, 10 minutes after block, mid-operative, and after extubation). Any adverse events, such as bradycardia or hypotension, were immediately dealt with.

When the procedure was finished, inhalational anesthesia was stopped, the minimal to moderate amount of blood and oral secretions in the oropharynx were carefully suctioned, and reversal agents (atropine 10-15µg/kg and neostigmine 0.05 mg/kg) were administered once the neuromuscular blockade had sufficiently recovered and adequate spontaneous breathing had been regained. An infant who was awake, presented with regular breathing and had good muscle tone underwent extubation after his or her airway reflexes had returned.

Patients were then transported to the Post-Anesthesia Care Unit (PACU) when they were stable from both cardiovascular and respiratory standpoints. A pediatric anesthesiologist and nurse, who were blinded to the study methodology, observed them. Hemodynamic measurements were recorded in the PACU at Minute 30, as well as at intervals of 1, 2, 4, 6, 12, and 24 h starting from the time of patient arrival. The child was discharged to the ward after meeting the standard discharge criteria.

FLACC scale 15 was used by a blinded observer anesthesiologist to assess pain in patients during the first 24 h (ranging from 0–10, where 0 = no pain, 10 = worst pain), at the time of arrival to the PACU, at postoperative minute 30, and then at 1, 2, 4, 6, 12 and 24 h.

Acetaminophen was administered intravenously at a dosage of 10 mg/kg whenever the FLACC Score was greater than 4. If the FLACC score was ≥ 4, the dose was repeated every six hours until they could tolerate oral intake. The time to the first analgesic requirement and the total acetaminophen consumption over the first 24 h postoperatively were recorded.

The Pediatric Anesthesia Emergence Delirium (PAED) scale 16 was used to measure the incidence of emergence agitation at 0, 5, 10, 20, 30, and 60 min. Additionally, postoperative vomiting (POV) within the first 24 h following surgery was noted. If POV developed, ondansetron 0.1 mg/kg was prescribed intravenously.

Hypotension, bradycardia, shivering, and respiratory depression were among the other adverse side effects that were noted. The primary outcome was the time to the first analgesic request, while the secondary outcomes
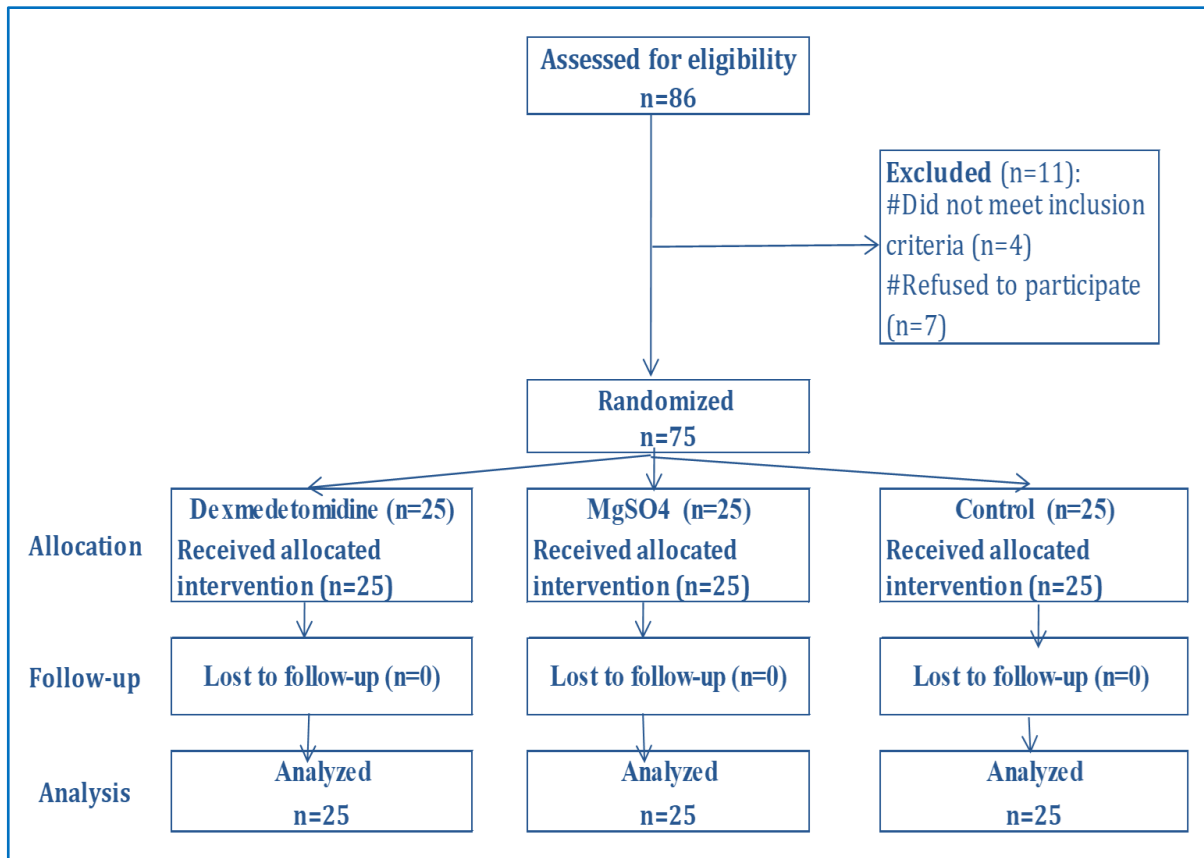
Figure 2: Flow chart of the studied cases

were the total amount of acetaminophen consumed in the first 24 h following surgery, pain assessments, and adverse drug reactions.

Sample size calculation

Using the STATA program, the sample size was calculated with the type 1 error (α) set to 0.05 and the power (1-β) set to 0.9. The result from a previous study by Sayed et al.,[17] showed that there was a significant difference between the study groups concerning the frequency of acetaminophen administrations; as 63% of cases in the Group D had paracetamol more than one time, compared to only 13% of patients of Group M. Calculation according to these values produced a sample size of 22 cases per group. To compensate for drop-outs, we included 25 cases in each group (a total sample of 75 cases).

Statistical methodology

The gathered data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software, version 28.0, IBM Corp., Chicago, USA, 2021. Shapiro-Wilk test was used to determine the normality of quantitative data, which was followed by mean and SD (standard deviation)

descriptions and an ANOVA test to compare them. For variables with low expected values, Fisher's Exact and Chi-Square tests were used to compare qualitative data that are expressed as numbers and percentages. Pairwise comparisons were made by using the post hoc Bonferroni test. P < 0.050 was considered significant.

3. RESULTS

The study's eligibility requirements were checked on 86 patients. Four patients did not meet the inclusion criteria, and seven patient guardians declined to participate, resulting in the exclusion of eleven patients. In the end, 75 patients—25 for each group—completed the study and their data were analyzed (Figure 2).

Patients in the three groups didn't differ regarding their demographic data (age, weight, sex, ASA-PS), repair type, and duration of surgery or anesthesia (Table 1).

There was no significant difference in all groups regarding HR and MBP in the intraoperative time (baseline, after intubation, 10 min after block, and mid-operative) as well as from postoperative min-0 to 4 h. HR and MBP at 6, 12, and 24 h were the lowest in the Group D, followed by the Group M, and the highest in the

Table 1. Comparison regarding baseline characteristics

Variables		Group D (n = 25)	Group M (n = 25)	Group C (n = 25)	p-value
Age (y)	< 1	15 (60.0)	16 (64.0)	14 (56.0)	#0.846
	1 – 7	10 (40.0)	9 (36.0)	11 (44.0)	
Sex	Male	16 (64.0)	18 (72.0)	19 (76.0)	#0.637
	Female	9 (36.0)	7 (28.0)	6 (24.0)	
Weight (kg)		15.8 ± 5.3	15.9 ± 5.6	16.5 ± 3.4	^0.866
ASA (n, %)	I	19 (76.0)	22 (88.0)	19 (76.0)	#0.472
	II	6 (24.0)	3 (12.0)	6 (24.0)	
Repair type	Primary	18 (72.0)	20 (80.0)	17 (68.0)	#0.620
	Revision	7 (28.0)	5 (20.0)	8 (32.0)	
Duration of surgery (min)		100.7 ± 9.9	98.4 ± 9.6	96.1 ± 17.4	^0.444
Duration of anesthesia (min)		117.5 ± 10.3	115.8 ± 10.1	114.3 ± 17.3	^0.685

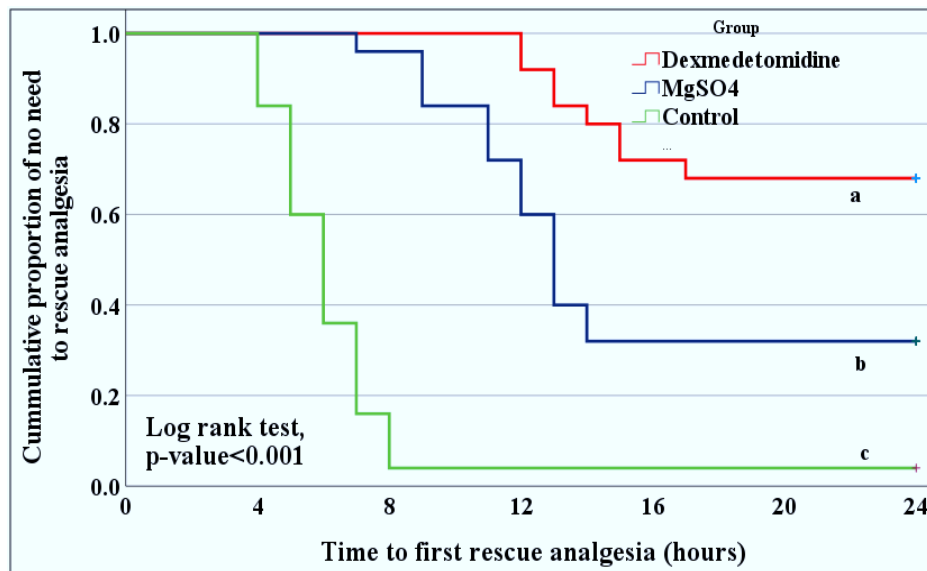*Data presented as Mean ± SD or n (%). ^ANOVA test. #Chi square test. §Fisher's Exact test.*

Figure 3. Comparison regarding postoperative pain perception (FLACC score) among the studied cases. *Significant

shortest in the Group C (13.9 ± 1.7 h, 11.5 ± 2.0 h, 5.9 ± 1.3 h) respectively (Figure 4).

In addition, the rate of analgesic doses was significantly less frequent in the Group D followed by Mgso4, and more frequent in the Group C.

Furthermore, total postoperative acetaminophen consumption was significantly lower in the Group D, followed by the Group M, and highest in the Group C (Figure 4).

Regarding postoperative side effects, emergence agitation, and POV were non-significantly less frequent in the Group D, followed by the Group M, and most frequent in the Group C. PAED scale at different time points was non-significantly lowest in the Group D, followed by the Group M, and highest in the Group C. Sedation was non-significantly most frequent in the Group D, followed by the Group M, and least frequent in the Group C. Bradycardia non-significantly occurred only in the Group D. Hypotension was non-significantly least frequent in the Group M, with equal incidences in Group D and Group C. Shivering was non-significantly most frequent in the Group C, with equal incidences in

Group C, the differences were significant only in the Group D at 6 h, while the differences were between all the study groups at 12 and 24 h.

Postoperative pain scores at different time points were non-significantly lowest in the Group D, followed by the Group M, and were the highest in the Group C, the differences were significant only in the Group C at 6 h, while the differences were between all the study groups at 12 and 24 h (Figure 3).

Time to first requested analgesia was significantly longest in the Group D, followed by the Group M, and

Table 2. The comparison regarding PAED score and postoperative side effects

Time		Group D (n = 25)	Group M (n = 25)	Group C (n = 25)	p-value
Emergence agitation		4 (16.0%)	5 (20.0%)	7 (28.0%)	#0.573
PAED scale	**Min-0**	6.8 ± 4.3	7.7 ± 4.7	8.0 ± 5.2	^0.612
	Min-5	6.0 ± 4.0	6.8 ± 4.5	7.1 ± 5.2	^0.652
	Min-10	4.4 ± 3.7	5.2 ± 4.0	5.8 ± 5.2	^0.488
	Min-20	3.2 ± 2.8	3.8 ± 3.5	4.2 ± 4.4	^0.618
	Min-30	1.8 ± 1.7	2.2 ± 2.7	2.7 ± 3.6	^0.535
	Min-60	0.7 ± 1.1	0.9 ± 1.5	1.2 ± 2.2	^0.596
Vomiting		1 (4.0)	2 (8.0)	4 (16.0)	§0.487
Sedation		4 (16.0)	2 (8.0)	0 (0.0)	§0.155
Bradycardia		3 (12.0)	0 (0.0)	0 (0.0)	§0.102
Hypotension		3 (12.0)	2 (8.0)	3 (12.0)	§0.999
Shivering		1 (4.0)	1 (4.0)	5 (20.0)	§0.200
Respiratory depression		0 (0.0)	0 (0.0)	0 (0.0)	NA

*Data presented as Mean ± SD unless mentioned otherwise. PO: Postoperative. NA: Not applicable. ^ANOVA test. *Significant. Homogenous groups had the same symbol "a,b,c" based on the post hoc Bonferroni test.*
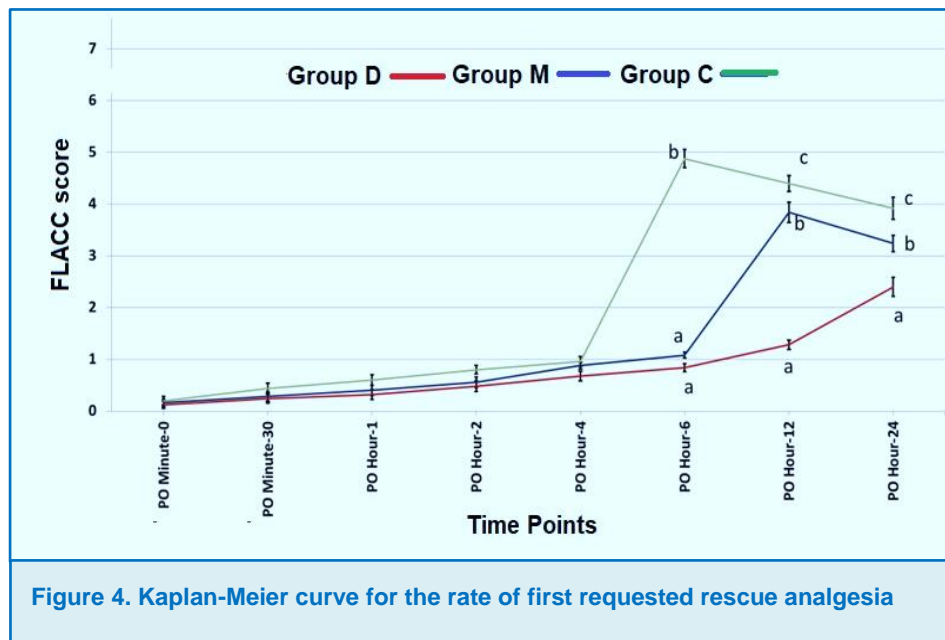
Figure 4. Kaplan-Meier curve for the rate of first requested rescue analgesia

Our results reported that the time to first request rescue analgesia was significantly increased in the dexmedetomidine group, followed by the $MgSO_4$ group, and shortest in the control group. The total acetaminophen dose needed was significantly lowest in the Group D, followed by the Group M, and highest in the Group C.

Opioids are widely used for the treatment of moderate to severe pain in pediatric patients, particularly in the immediate postoperative period. However, opioids are associated with a range of side effects, including nausea, vomiting, constipation, urinary retention, pruritus, sedation, respiratory depression, and opioid-induced hyperalgesia.[18,19,20] Opioid-sparing approaches to postoperative analgesia, including IONB should be considered to avoid the complications of opioids during postoperative recovery.

Group M and Group C. Respiratory depression did not occur in all studied groups (Table 2).

4. DISCUSSION

Perioperative pain management after cleft lip repair is very challenging, as the procedure is very painful and it's difficult to assess and manage pain at this age. We aimed for effective prolonged analgesia to avoid a vigorous child in pain which is considered as one of the risk factors for postoperative bleeding.

El-Emam EM at al.[21] compared Dex against dexamethasone as adjuvants for bupivacaine in IONB

and they noticed that Dex resulted in a more prolonged duration of analgesia and lower pain scores. Our study results are consistent with the study by Sumalatha G et al., who showed that 0.5 µg/kg Dex added to bupivacaine increased the duration of analgesia when compared to plain bupivacaine in IONB in children undergoing cleft lip surgery, and the number of patients who requested rescue analgesics were less.[22] Other studies supported our results, and proved that the addition of Dex to ropivacaine in supraclavicular brachial plexus block significantly prolongs the duration of analgesia.[23,24]

Dexmedetomidine and other alpha-2 selective adrenergic agonists are effective analgesics when combined with local anesthetics for peripheral blocks.[25] It inhibits current channels that help neurons return from a hyperpolarized state to their normal resting potential. Dex also selectively prevents C-fiber neurons from firing additional action potentials, causing analgesia. The majority of analgesic and sedative effects on the CNS are mediated by α2A-subtype receptors.[26]

On the other hand, the addition of $MgSO_4$ as an adjuvant to bupivacaine as explained by Verma V, et al., significantly prolongs the duration of analgesia and decreases the analgesic requirement in ultrasound-guided supraclavicular brachial plexus block.[27] Similarly, he concluded that $MgSO_4$ and ketamine were effective as adjuvants to levobupivacaine in erector spinae block for postoperative analgesia in breast cancer surgery, but with better analgesia provided by $MgSO_4$.

$MgSO_4$ is an N-methyl-d-aspartate (NMDA) receptor antagonist that works to reduce excitatory neurotransmission by restricting intracellular calcium levels through NMDA receptor antagonism.[29] Contrary to our results, Sayed et al. investigated and proved that magnesium had a prolonged analgesic effect compared with Dex.

We demonstrated in our results that postoperative pain perception at different time points was lowest in the Group D with a more frequent sedation level, followed by Group M and the highest pain perception with the least sedation level in the control group, Simultaneously, these differences were recorded by a systematic review and meta-analysis conducted by Vorobeichik et al. that perineural Dex was followed by excessive postoperative sedation that was recorded using many scales.[30] On the other hand, Obayah et al. did not demonstrate a sedative effect in their result but, this can be due to the heterogeneity of the scales used.[31]

Side effects demonstrated in our study as POV was non-significantly less frequent in the dexmedetomidine group, followed by the $MgSO_4$ group, and most frequent in the control group, and there were no other serious side

effects. Our results were concomitant with Elsonbaty M, et al.[32] who proved that, the IONB technique has minimal complication rate with greater parental satisfaction. Other researchers proved that Dex and $MgSO_4$ as adjuvants showed satisfactory pain relief without serious side effects. [21,28]

Our study recorded no relevant intraoperative and postoperatively cardiovascular events. The heart rate remained on the lower side in the Group D but did not require any intervention. Consistent with our results, the results of several studies have demonstrated that Dex can prolong analgesia significantly without inducing significant hypotension, or bradycardia.[21,31]

5. CONCLUSION

Our results suggest that there is a benefit of adding dexmedetomidine or MgSO4 to bupivacaine in IONB in cleft lip surgery. However, dexmedetomidine demonstrated superiority compared to MgSO4 concerning prolonged postoperative analgesia.

6. Data availability

The numerical data is available with the corresponding author and can be provided on request.

7. Conflict of interests

9. Ethical approval

This prospective, randomized, clinical study was approved by the University of Ain Shams Institutional ethics board review (FMASU R176/2022).

10. Authors' contribution

MA: Concept, data collection, data analysis, literature search, revised and approved the manuscript.
AA, MM and MA: Designed the study protocol, manuscript writing and editing, literature search, revised and approved the manuscript.

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