Research article

Effect of intravenous magnesium sulphate or dexamethasone as adjuvants to sevoflurane anesthesia to prevent delirium during primary cleft palate repair, controlled randomized blind study

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ABSTRACT

Background: Emergence delirium (ED) is a frequent postoperative complication in young children undergoing cleft palate repair and it may be exacerbated by sevoflurane anesthesia.
Objective: This study was undertaken to study the effect of magnesium sulphate or dexamethasone as adjuvants to sevoflurane in decreasing the delirium after primary cleft palate repair.
Patients and methods: 90 patients undergoing primary cleft palate repair were randomized into 3 groups equally. Controlled group (group C): continue without any addition, Magnesium group (group M): 30 mg/kg loading dose on 10 min then 10 mg/kg every one hour though the operation and Dexamethasone group (group D): 0.15 mg/kg single dose after induction. During the study period, heart rate, mean arterial blood pressure, postoperative delirium, blood glucose level and nausea were recorded for 120 min.
Results: The heart rate and blood pressure were significantly decreased in group M and group D, than the control group. Significant lower postoperative delirium and nausea in group D and M in comparison with control group although D group had the best effects.
Conclusion: Co-administration of intravenous magnesium sulphate or dexamethasone with to sevoflurane anesthesia during primary cleft palate repair provides more vital hemodynamic state and decrease in postoperative vomiting and delirium when compared with control group.
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1. Introduction

Cleft palate repair in children is a common pathological craniofacial abnormality condition that characterized by critical postoperative pain [1,2]. This surgery needs general anesthesia and effective pain management during and after surgery in children as it can result in delirium (emergence agitation) [1,3].

Although sevoflurane is associated with a major delirium in the recovery phase, it is the most popular drug of choice in children for general anesthesia. It has a very attractive characteristics for anesthesiologists in comparison with other volatile anesthesia as low kidney and liver toxicity, low blood/gas partition coefficient, less effects on heart rate and less irritant to the airway [4,5].

As for patients and their parents, the delirium is considered a significant source of satisfaction as the children became irritable, vigorous crying and kicking, nausea and vomiting, as well as pulmonary complications and dehiscence of wound that requires special care from both nurses and parents as well as using analgesic medications, that increase the hospital stay of the patients [6,7].

Magnesium sulphate is very effective adjuvant for general surgery that is used for its antiarrhythmic effect and in prevention of febrile seizures recurrence [8]. Magnesium is also used for management of severe pain and immediate recovery agitation as it has a detoxifying, antinociceptive and sedative effect [9–11].

Dexamethasone (DEX) is a glucocorticoids with an analgesic, sedative and anti-inflammatory effects [12]. DEX has been used effectively in infant surgeries in order to prolong the time of analgesia and decreasing the post-operative nausea and vomiting [13,14].

The hypothesis of this study is that anesthetic adjuvants can prolong the duration of analgesia hence decreasing postoperative pain and agitation [15] thus this study was conducted to investigate the efficiency and compare between administration of intravenous (IV) dexamethasone or magnesium sulphate to prevent immediate postoperative agitation, haemodynamic effect, postoperative complications and blood glucose level in children undergoing primary cleft palate repair.

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2. Patients and methods

This is a randomized double blind controlled trial that was conducted at Cairo University Specialized Children's Hospital and Benha university hospitals between April 2015 and December 2015.

Local ethical committee approval and parent's informed written consent were taken before enrollment in the study.

To study the effect of Magnesium sulphate or Dexamethasone as adjuvants to sevoflurane in decreasing the delirium in children after primary cleft palate repair, we conduct this study comparing Magnesium (Group M) and Dexamethasone (Group D) with control (Group C). Inclusion criteria were all children with incomplete cleft palate, 2–6 years old and ASA I or II physical status. Patients with known hypersensivity to used drugs or complaining of cardiac, neurological, renal disorders were excluded.

In Group M, 30 mg/kg loading dose of Magnesium sulphate was given on 10 min then 10 mg/kg every one hour though the operation. In Group D, Dexamethasone 0.15 mg/kg was given as a single dose after induction while the control group was continued without any addition.

Patients were randomized by using on line randomization program (http://www.randomizer.org/) and concealed using sealed, opaque envelopes. The allocation was revealed by the operating surgeon by opening the top envelope before surgery. Patients and data collectors not present in the operating theater were blinded to assignment of patients.

Prophylactic atropine 0.01 mg/kg and midazolam 0.02 mg/kg were given intramuscular. Induction of anesthesia was done by inhalation sevoflurane 5% in 100% oxygen for 2 min and intravenous catheter inserted. Monitors were fixed (ECG, noninvasive blood pressure, pulse oximeter, capnography and temperature probe). Maintenance was done by atracurium 0.5 mg/kg and sevoflurane 1.7%, fentanyl 1 mg/kg. Intubation was done by appreciate size endotracheal tube and controlled ventilation was adjusted to maintain end tidal CO_2 between 35 and 40 mmHg.

At the end of surgery, sevoflurane was discontinued and neuromuscular blocker was reversed by atropine 0.01 mg/kg and neostigmine 0.05 mg/kg intravenously.

1. Primary outcome:
   The emergence of delirium was assessed using Watcha score at 5 & 10 min postoperative (Table 1) [16].
2. Secondary outcomes:
   a. Heamodynamic measurement: mean arterial blood pressure and heart rate were measured at preinduction and every 10 min.
   b. Blood sample was taken from start the operation and every 30 min. for 2 h to determine glucose level.
   c. Postoperative nausea and vomiting were also recorded between the groups.

Sample size estimation was performed according to a pilot study of the first 8 patients to detect Watcha score (primary outcome) of 10% between the control group and study groups with alpha error 0.05 and a power of 80%. The effect size was 0.804.

Minimum adequate sample size was 26 in each group. We considered 30 patients in each group to overcome the dropout.

Statistical analysis of data was done by using SPSS version 16. The qualitative data were described as numbers and percentages and were analyzed by using Chi-square test, while quantitative data were expressed as mean ± SD and analysis of data was done using ANOVA test. For significant ANOVA test, post hoc analysis was done to detect the significant group. P-Value ⩽ 0.05 was considered significant.

3. Results

In total 106 patients were screened during the study period. 11 patients did not match the inclusion criteria. 5 patients refused to participate. So in total 90 patients completed the study protocol (Fig. 1).

Demographic characteristics were non comparable among groups (Table 2).

As for the heart rate, there were no statistically significant difference among groups at baseline and at 10 min. The heart rate was significantly different between groups in comparison with the control group from 20 min till 120 min. Also, there was statically significant difference between group M and group D from the 40 min till 120 min. The heart rate was significantly decreased in M group in comparison with group D where the pulse was increased but still lower than control group (Fig. 2).

MAP was comparable among groups at baseline, 10 min. and 20 min. At 30 min, there was a significant decrease in MAP in group M and group D in comparison with the control group. From 40 min till 120 min, group M showed the lowest decrease in MAP in comparison with the two other groups (Fig. 3).

There was no statistically significant difference in the blood glucose level between groups (Fig. 4).

Agitation score in the D group and group M was significantly lower in comparison with the control group at 5 min and 10 min (Tables 3 and 4) but it is insignificantly lower in group D in compare to group M.

Regarding the incidence of nausea, group D had the lowest incidence followed by group M in comparison with the control group (Table 5).

4. Discussion

The most common congenital facial malformation is the cleft lip and palate in humans that is also called a part of a syndrome when its incidence is connected with other congenital defects. Its epidemiology differ in accordance to the geographic and ethnic variation [17]. This disorder is generally divided into two groups including the isolated cleft palate and clefts involving the lip with or without cleft palate [1].

After sevoflurane anesthesia of cleft palate repair surgery, many factors can contribute to the high rate of emergence agitation in infant patients and these factors may include; skill of anesthesia management, surgical procedure, incapacity and loss of independence, separating from the family as well as sevoflurane itself. [1].

Non efficient analgesia in the post-operative emergence period may be the cause of agitation with special regard to the short surgical procedures for which peak effects of analgesics may be delayed until the child is completely awake [18]. Since postoperative and pain is considered to be one of the major causes of EA, therefore, it is generally believed that reducing or eliminating pain may decrease the incidence of EA. It has been reported in several previous studies that regional block, opioids, and non-steroidal anti-inflammatory drugs could decrease the incidence of EA [19–21].
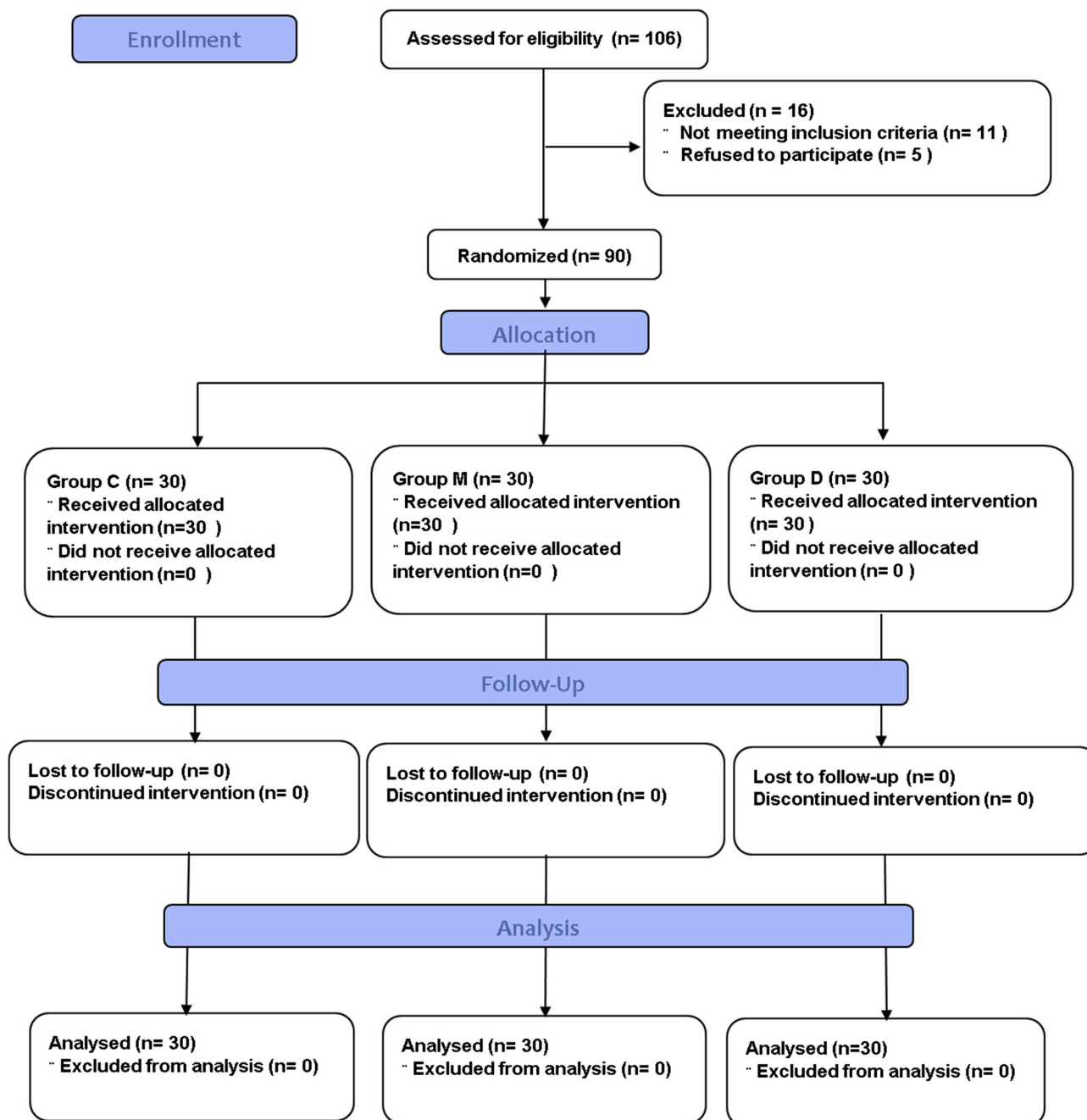
Table 1
Watcha score. Score is observed values (16).

Score	Behavior
0	Asleep
1	Calm
2	Crying, but can be consoled
3	Crying, but cannot be consoled
4	Agitated and thrashing around

Figure 1. Consort flow diagram.

Table 2
Demographic characteristics of patients.

		Group C	Group M	Group D	p-value
Age (yrs.)		3.6 ± 1.16	3.76 ± 1.2	3.7 ± 1.36	0.87
Weight (kg)		12.03 ± 2.3	12.37 ± 2.5	11.6 ± 1.93	0.45
Sex	M	12	17	14	0.42
	F	18	13	16	

Concerning delirium, it was found that the incidence of agitation in M group was significantly lower than control group. In agreement, the use of IV bolus of magnesium sulphate during adenotonsillectomy with sevoflurane anesthesia in children was found to significantly decrease the occurrence and severity of delirium [7]. Also, the scores of agitation were higher in the control com-

pared with the magnesium group with a significant difference at all assessment points in the PACU [22]. A recent studies proposed the same idea as magnesium sulphate caused a significant reduction in sevoflurane-induced EA with no delay in patient discharge [24,29]. The efficiency of magnesium in decreasing the postoperative pain and delirium could be attributed to its action as NMDA
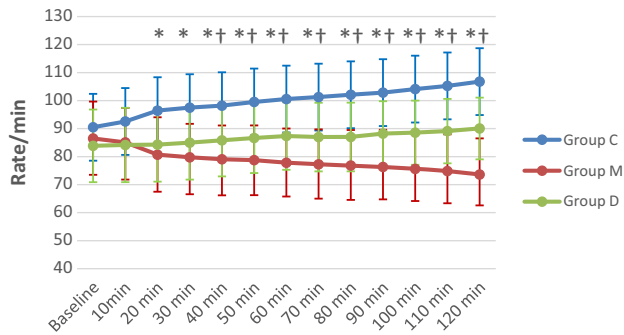
Figure 2. Heart rate *Significant in comparison with the control group. †Significant between group M and Group D.
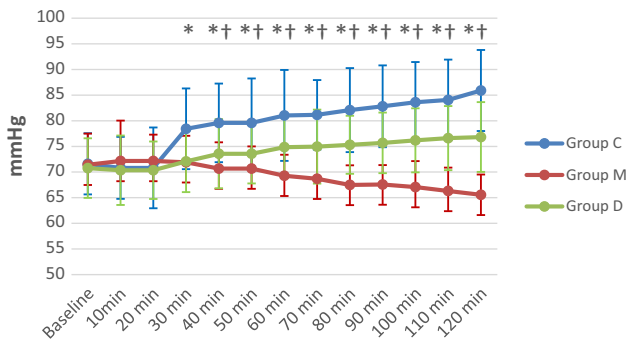

Figure 3. Mean arterial blood pressure *Significant in comparison with the control group. †Significant between group M and Group D.
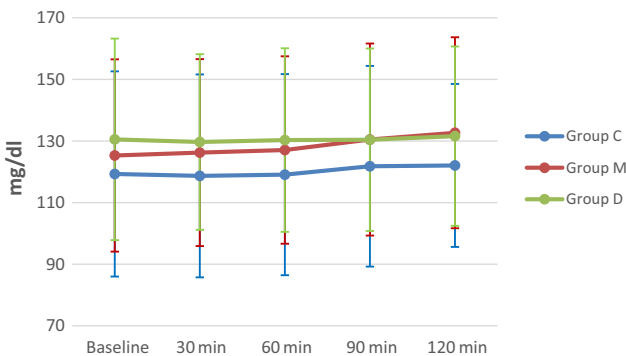

Figure 4. Blood glucose level.

Table 3
Watcha score at 5 min.

Score	Group C	Group M	Group D	P-value
0	1(3.3%)	8(26.6%)	9(30%)	<0.001
1	1(3.3%)	10(33.3%)	12(40%)	
2	6(20%)	7(23.3%)	6(20%)	
3	12(40%)	4(13.3%)	3(10%)	
4	10(33.3%)	1(3.3%)	0	

receptor antagonist [30–32]. In contrast, Apen et al. found no influence of a magnesium sulphate infusion 10 min prior to the end of adenotonsillectomy surgery on emergence agitation after sevoflurane anesthesia [33].

On the other hand and according to our knowledge, there is no study that has evaluated dexamethasone effect on delirium incidence after cleft palate repair surgery but this study found that

Table 4
Watcha score at 10 min.

Score	Group C	Group M	Group D	P-value
0	0	7(23.3%)	8(26.6%)	<0.001
1	2(6.6%)	9(30%)	10(33.3%)	
2	6(20%)	8(26.6%)	7(23.3%)	
3	11(36.6%)	5(16.6%)	4(13.3%)	
4	11(36.6%)	1(3.3%)	1(3.3%)	

Table 5
Incidence of nausea.

	Group C	Group M	Group D	p-value
Positive	14(46.6%)	10(33.3%)	3(10%)	<0.001
Negative	16(53.4%)	20(66.7%)	27(90%)	

delirium was significantly decreased in dexamethasone group when compared with control and even M group and this could be attributed to the mechanism of action of glucocorticoids through inhibiting the inflammatory mediators production as bradykinin and prostaglandin as well as prevention of pain threshold reduction which occurs in surgeries and reducing tissue swelling due to its associated anti-inflammatory effects and therefore inhibit nerve compression by inflammatory tissue [34,35]. There are numerous studies showed the efficiency of dexamethasone antiemetic and analgesic properties in different surgeries such as caesarean section, tonsillectomy and cardiac surgery [36–38]. Bisgaard et al., found that the preoperative intravenous administration of dexamethasone has been reported to reduce postoperative pain [39]. Also, the intravenous dexamethasone (0.2 mg/kg) and oral acetaminophen codeine (20 mg/kg) can significantly decrease the incidence and severity of agitation but does not have an effect on postoperative pain in children undergoing adenotonsillectomy [40].

During the study, the pulse and blood pressure were significantly decreased in M group in comparison with control and D group. In consistence, Magnesium sulphate infusion was associated with stable mean arterial blood pressure and a reduced heart rate while the control group has a higher pulse than Magnesium sulphate group [22]. A similar haemodynamic profile was recently reported with the use of magnesium sulphate for the management of status asthmaticus in paediatric patients [23]. Also, Bondok and Ali (2014) showed a significant stabilization in the heart rate and the systolic blood pressure during the removal of LMA and emergence in group M compared with group C [24]. In addition, there was a significant decrease in heart rate intraoperatively (T3) and postoperatively (T4) (P < 0.05) in the magnesium group when compared with the control group [7]. Moreover, James (2009) showed a reduction in blood pressure that could be associated with $MgSO_4$ vasodilatory effect [25].

This study also demonstrated that the control group showed a higher increase in the pulse and blood pressure than dexamethasone group with a statistically significant difference. These results were in agreement with a recent study that demonstrated that heart rate, systolic and diastolic blood pressure were significantly higher in the control group compared to dexamethasone and fentanyl group following incision at 1, 5, 20 and 30 min [26].

In partial consistence with these results, the heart rate and systolic and diastolic blood pressure were increased in control group than dexamethasone group but with no significant association with neither pulse nor blood pressure [27,28].

As regarding occurrence of nausea and vomiting our results showed that there was a statistically significant difference between the three group according to occurrence of nausea as group D was the least drug showing positive nausea followed by M group in comparison with the control group.

In accordance, the incidence of postoperative vomiting was significantly less in the dexamethasone group [28]. This is in agreement with several previous studies that showed that dexamethasone decreases the incidence of postoperative nausea and vomitting [41–43]. In contrast, dexamethasone had no significant effect on the incidence or severity of postoperative nausea and vomiting after induction and maintenance of anesthesia with sevoflurane [44]. While in Mg group another study found no significant difference between M group in comparison with the control group after sevoflurane-based anesthesia in children [29].

5. Conclusion and recommendations

The presently conducted randomized controlled study, showed that either adding magnesium sulphate or dexamethasone to general anesthesia administered sevoflurane could decrease the postoperative delirium and vomiting as well as showing better hemodynamic state than the control patients. Also, the dexamethasone group was accompanied by superior decrease in the incidence of delirium when compared with M and C group. Further evaluation of the safety and efficiency of Magnesium Sulphate and Dexamethasone in decreasing delirium in children undergoing cleft repair should be studied in large population studies.

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