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Research Article

Feasibility of adding magnesium to intrathecal fentanyl in pediatric cardiac surgery

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KEYWORDS

Intrathecal;
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Abstract *Background:* Magnesium is (NMDA) receptor antagonist used as an adjuvant for post-operative analgesia. There are several studies comparing the efficacy of the different routes of administration of magnesium. We aimed to study the effects of adding magnesium to IT fentanyl on peri-operative analgesic requirements after elective pediatric cardiac surgery.

Methods: This prospective double controlled randomized study (closed envelop method) included eighty pediatric patients subjected to elective open cardiac surgery. They were randomly allocated into four equal groups (20 patients each): (A) *control group* (i.v. fentanyl), (B) *intrathecal fentanyl group* (ITF) (received IT 1 μg/kg of fentanyl), (C) *intrathecal fentanyl and magnesium (0.5 mg/kg) group* (received IT 1 μg/kg of fentanyl citrate and 0.5 mg/kg magnesium sulfate), and (D) *intrathecal fentanyl magnesium (1 mg) group* (received IT 1 μg/kg of fentanyl citrate, and 1 mg/kg magnesium sulphate). The perioperative anesthetic management was standardized.

Results: The results of this study demonstrated that the analgesic profile tended to be better with ITF, ITF-Mg 0.5 mg/kg and ITF-Mg 1 mg/kg groups than the control group. Also, intraoperative fentanyl used in ITF-Mg (1 mg) was statistically less as compared with ITF and ITF-Mg (0.5 mg)

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groups. Time to extubation (h) was surprisingly, shorter in ITF-Mg (1 mg) as compared with ITF and control groups. Also, postoperative intravenous fentanyl consumption μg/kg/24 h was more in control group as compared with other groups.

Conclusion: In conclusion, the use of intrathecal fentanyl-magnesium (1 mg/kg) in pediatric patients subjected to open cardiac surgery reduced intra and postoperative analgesic consumption, prolonged the time to first analgesic requirement and allowed early tracheal extubation when compared with intravenous fentanyl, intrathecal fentanyl or intrathecal fentanyl-magnesium (0.5 mg/kg).

1. Introduction

Several retrospective studies concerning the feasibility of an early extubation approach in pediatric cardiac patients were published, including patients at high risk for a complicated perioperative course [1,2]. The advantages of this approach may be primarily related to the avoidance of adverse effects of prolonged mechanical ventilation and lower hospitalization costs related to shorter ICU and hospital stay [2].

Intrathecal (IT) morphine has delayed the onset of action and may cause delayed extubation after cardiac surgery because of prolonged ventilatory depression [3]. On the contrary, lipid-soluble opioids such as fentanyl and sufentanil have a rapid onset but shorter duration of action [4].

Magnesium has antinociceptive effects in animal and human models [5]. These effects are primarily based on the regulation of calcium influx into the cell, which is natural physiological calcium antagonism, and antagonism of the *N*-methyl-D-aspartate (NMDA) receptor [6]. There are some studies comparing the efficacy of the different routes of administration of magnesium, such as i.v., IT, or epidural and its effect on anesthetic and analgesic quality. Intravenous magnesium, even high doses, is associated with limited passage across the blood–brain barrier [7,8]. Studies in humans in which IT magnesium was given to various groups of patients found that none had symptoms suggestive of neurotoxicity, nor did they exhibit signs of systemic toxicity such as hypotension, dysrrhythmia, somnolence or weakness, and even on long term follow up [9–13].

Buvanendran et al. (2002) found that intrathecal 50 mg magnesium prolongs spinal fentanyl analgesia during labor and suggested that the availability of an intrathecal NMDA antagonist could be of clinical importance for pain management [9]. Also, Bilir et al. (2007) found that co-administration of epidural magnesium for postoperative epidural analgesia provided a pronounced reduction in patient-controlled epidural fentanyl consumption without recorded side-effects [7].

This study hypothesized that preoperative administration of IT fentanyl, and magnesium in different doses in pediatrics undergoing open heart surgery for congenital heart diseases may facilitate the weaning from CPB, improve the quality of postoperative analgesia, decrease stress response and shorten the extubation time. The aim of this study is to compare the effects of both IT fentanyl and IT fentanyl-magnesium in two different concentrations on peri-operative analgesic requirements, weaning from cardiopulmonary bypass, stress response and the extubation time in elective pediatric cardiac surgery.

2. Materials and methods

After approval of the local ethical committee of Anesthesia And Surgical Intensive Care Department, Mansoura University, this prospective double controlled randomized study (using closed envelop method) was conducted on 80 patients of either sex, aged 4–14 years submitted for elective cardiac surgery (VSD, ASD, Subaortic membrane) from 2007 to 2010 using CPB at Pediatric Cardiac Surgery Unit in Children Hospital, Mansoura University. All parents of the patients signed written informed consent prior to enrollment after explanation.

Exclusion criteria include: coagulopathy, platelet count $< 100{,}000/mm^3$, and the recent use of anticoagulant drugs. Also, redo surgery, heart block, pulmonary hypertension, preoperative impaired left ventricular ejection fraction $< 40\%$ were excluded. Patients with signs of interstitial or alveolar edema on chest X-ray, body mass index $> 35\ kg\ m^{-2}$, preoperative serum creatinine > 1.5 mg/dl, hypo and hypermagnesemia were also excluded from the study. Known or anticipated difficult airway, scoliotic spines, myopathies, current use of clonidine or steroids (for their possible confounding effects on postoperative analgesia), and any known contraindication to spinal anesthetic administration were not included.

All patients were subjected to preoperative clinical examination for assessment of cardiovascular function. Laboratory investigations including CBC, electrolytes analysis; ABGs, urine analysis, and coagulation survey were done. Blood glucose level, liver and renal function tests were tested. Radiological work, ECG and echocardiographic investigations were fulfilled. Patients were randomly classified using closed envelop method into four equal groups: A – Control group: ($n = 20$) no intrathecal drugs. B – ITF (fentanyl) group: ($n = 20$) intrathecal fentanyl 1 μg/kg. C – IT fentanyl-magnesium (0.5 mg/kg) group: ($n = 20$) intrathecal fentanyl 1 μg/kg with magnesium sulfate 0.5 mg/kg. D – IT fentanyl-magnesium (1.0 mg/kg) group]: ($n = 20$). Intrathecal fentanyl 1 μg/kg with magnesium sulfate 1 mg/kg. In All Groups anesthesia was maintained with both isoflurane and intravenous fentanyl. All injectate was given 0.15 ml/kg as whole volume in preservative free sterile water up to maximum volume 4 ml regardless to more body weight. All children fasted according to the fasting protocol with age for at least 4 h before the surgery. All patients were pre-medicated in the preoperative area with I.M. 0.05 mg/kg midazolam and 0.015 mg/kg atropine sulfates 15 min before induction of general anesthesia. Five leads ECG, peripheral oxygen saturation [SpO_2] and non-invasive blood pressure [NIBP] were monitored. Supplemental oxygen was provided via a face mask. Peripheral intravenous indwelling cannula was inserted one hour after application of EMLA cream.

In all groups, Anesthesia was induced by slow i.v. administration of fentanyl 10 μg/kg, propofol 1–2 mg/kg, and 0.1 mg/kg vecuronium to provide neuromuscular blockade and facilitate tracheal intubation. With loss of consciousness, posi-

tive pressure ventilation was started via face mask at a rate of 20–28 breathings per minute. Patients were intubated orally with an appropriately sized endotracheal tube such that no audible air leak was present below 35 cm H_2O peak inspiratory pressures.

Patients were mechanically ventilated with 100% O_2 and the end-tidal CO_2 was monitored by main-stream capnogram and maintained between 30 and 35 mmHg.

Anesthesia was maintained with isoflurane, incremental 0.02 mg/kg doses of vecuronium to maintain muscle relaxation and additional i.v. boluses of fentanyl (1 μg/kg) were given if blood pressure and heart rate increased (>25% above baseline) and it was assumed that the increases were due to insufficient depth of anesthesia, hypotension was considered clinically significant when systolic arterial blood pressure differed by more than 25% compared with the baseline values for more than 1 min and was treated with intravenous fluids and, when indicated, incremental doses of ephedrine, while bradycardia was considered clinically significant when heart rate decreased by more than 25% compared with baseline values for more than 1 min and was treated with atropine intravenously.

A radial artery catheter (22–24 G) was inserted, after performance of a modified Allen's test in the non dominant hand, to monitor the arterial blood pressure and blood gases sampling during the entire procedure. A urinary catheter was placed to monitor urine output. Also, rectal and nasopharyngeal temperatures were continuously monitored; an appropriate size central venous catheter was inserted under complete aseptic conditions for central venous pressure monitoring [insertion done after intrathecal injection to allow maximum time (more than 60 min) between intrathecal and heparin injection].

The patient was placed in the right lateral decubitus position. The skin over the injection area was cleaned with chlorohexidine 0.5% containing solution, which was allowed to dry. Then, using a sterile technique a 2-inch, 25-gauge Quincke spinal needle was inserted at L3–4 or L4–5. Successful dural puncture was confirmed by observation of a free flow of cerebrospinal fluid, and the injection was performed with the bevel of the needle oriented in the cephalic direction and the table turned with head up position for 5 min [hypobaric solution (specific gravity measured for different injectant solution using combitest strips and was about 1000–1005 for fentanyl in water and about 1005 for both fentanyl-0.5 mg magnesium and fentanyl-1 mg magnesium)] to get high level (the injectate was unknown to the anesthetist in charge, monitoring done by the anestheist out of the study, and randomization was done through closed envelop method).

H.R, MAP, CVP, $EtCO_2$, SpO_2, nasopharyngeal and rectal temperatures, arterial blood gases and electrolytes (Na and K), were recorded at the following time intervals: Before induction of general anesthesia (baseline), after induction, after skin incision, after sternotomy, and then each 15 min after discontinuation of cardiopulmonary bypass. Hypertension and hypotension were considered clinically significant when systolic arterial pressure differed by more than 25% compared with baseline values for more than 1 min. Bradycardia was considered clinically significant when heart rate decreased by more than 25% compared with baseline values for more than 1 min. ACC (minutes), CPB (minutes), spontaneous recovery of the heart, need for DC shocks and the inotropes ± dilators/vasopressors or support to wean the heart from CPB were recorded in all the patients.

After surgery, patients were transferred to the ICU, where they were monitored by the other team who were blinded to the anesthetic protocol that had been used. In the ICU. H.R, MAP, CVP were recorded at one hour intervals after admission to ICU, for 12 h, then every 2 h for 24 h.

Post – extubation hourly pain score was assessed using objective pain discomfort score (10 points scale; where 0 = no pain & 10 = maximum pain) in children for 12 h [14].

Bromage score, was assessed after extubation and graded as: I – Free movement of legs and feet [Nil (0%)], II – Just able to flex knees with free movement of feet [Partial (33%)], III – Unable to flex knees, but with free movement of feet, [Almost complete (66%)], IV – Unable to move legs or feet [Complete (100%)].

Extubation time and the need for reintubation were recorded. Criteria for extubation included a responsive and cooperative patient, negative inspiratory force of >20 cm H_2O, vital capacity >10 ml/kg, PaO_2 >80 mmHg with fraction of inspired oxygen <0.5, pH >7.3, core temperature >36.5 °C, hemodynamic stability, limited chest tube drainage and no uncontrolled dysrrhythmia. First request for analgesic requirement and the total dose of analgesic consumption [i.v. fentanyl μg/kg], the length of ICU and hospital stays were recorded. Neurological evaluation was done on a daily basis to exclude any signs of neurological abnormality. Incidence of nausea, vomiting, retention, or pruritus, as signs of opioid side effects was recorded.

In this study, the Stress response to surgery and CPB was determined by changes in serum cortisol, and blood glucose concentrations. Venous blood samples were collected at four times: preoperatively, 5 min after sternotomy, 1 and 24 h after CPB. These times were based on likely physiological responses over time and local economic limitations. The blood samples were centrifuged and serum was drawn off and was stored at 4 °C until assayed within 2 weeks of collection. Serum cortisol levels were determined using a radioimmunoassay technique (Streptavidin Coated microparticles). The sensitivity (Lower detection limit) is 0.018 μg/dL (0.5 nmol/dL) and the coefficient of variation 9%.

Serum magnesium level was measured preoperative (24 h before surgery) to make sure normal serum level and postoperative (6 h after surgery to decrease hemodilution effect of CPB priming), to exclude any systemic effect of intrathecally given magnesium.

The statistical analyzes of data were done by using excel program and *SPSS* (SPSS, Inc, Chicago, IL.) program statistical package for social science version 10. Data distribution K-S (Kolmogorov-Smirnov) test was used to test significant nonparametric data. The analysis of the data was done to test statistical significant difference between groups. ONE WAY ANOVA test to compare more than two groups, followed by Post Hoc test LSD (least significant difference) for inter groups comparisons. For quantitative data student *t*-test was used. Paired sample *t*-test was done to compare significance in one group at different times. Chi square test was used for qualitative data. P value was considered significant if <0.05 at confidence interval 95%.

Table 1 Patient's characteristics in the studied groups. Data are expressed as mean ± SD and number.

	Control group (n = 20)	ITF group (n = 20)	ITF-Mg (0.5 mg) group (n = 20)	ITF-Mg (1 mg) group (n = 20)
Age (year)	6.28 ± 1.94	5.04 ± 0.51	5.86 ± 1.34	5.91 ± 1.62
Body mass index (kg/m^2)	18.33 ± 5.18	22.13 ± 6.04	17.40 ± 4.09	19.53 ± 6.89
Gender (M/F)	12/8	13/7	11/9	13/7
Surgical procedure				
ASD	10	11	9	10
VSD	8	8	9	8
Subaortic membrane	2	1	2	2

3. Results

Table 1 showed the patients demographics of the four studied groups, control group (i.v.), ITF group, ITF-Mg (0.5 mg) group, and ITF-Mg (1 mg) group, there were no significant differences between the four groups as regards age, body mass index (BMI), male to female ratio and the type of surgical procedure.

In this study intraoperative parameters, [ACC (min), CPB (min), lowest temperature on CPB (°C), and operative time (min)] showed no significant differences between the four groups but the total dose of intraoperative i.v. fentanyl used was significantly less in ITF group, ITF-Mg (0.5 mg) group, and ITF-Mg (1 mg) group when compared with the control group (15.60 ± 2.84 in ITF, 14.40 ± 2.02 in ITF-Mg (0.5 mg), 11.26 ± 1.38 in ITF-Mg 1 mg, as compared with 18.06 ± 2.43 in control group). Also, Intraoperative fentanyl used was significantly less in group ITF-Mg (1 mg) as compared with ITF group, and ITF-Mg (0.5 mg) group (Table 2).

In this study, no significant differences between the four groups as regard to criteria of weaning from CPB (Table 3).

Most of the patients in the four groups were extubated early (within 6 h). However, the number of patients, who fulfilled the extubation criteria in the operating room was significantly more in the ITF-Mg (1 mg) group (6 patients) when compared with the other groups (none) as, time to extubation (h) was shorter in ITF-Mg (1 mg) as compared with ITF and control groups (1.84 ± 0.57 in ITF-Mg 1 mg, 4.80 ± 1.43 in control, and 4.10 ± .84 in ITF groups) (Table 4). Also, time to 1st analgesic requirement (h) was shorter in control group when compared with other groups (7.30 ± 2.02 in ITF, 8.42 ± 2.04 in ITF-Mg 0.5 mg, 10.33 ± 5.36 in ITF-Mg 1 mg, and 2.86 ± 1.64 in control groups), and it was statistically longer in ITF-Mg (1 mg) as compared with ITF and

Table 2 Intraoperative variables in the studied groups. Data are expressed in mean ± SD.

	Control group (n = 20)	ITF group (n = 20)	ITF-Mg (0.5 mg) group (n = 20)	ITF-Mg (1 mg) group (n = 20)
ACC (min)	29.00 ± 6.81	27.00 ± 5.41	29.26 ± 12.61	29.53 ± 7.18
CPB (min)	43.00 ± 6.72	44.06 ± 7.77	44.40 ± 16.07	45.26 ± 9.39
Minimum temperature on CPB (°C)	32.06 ± 1.75	32.26 ± 1.79	31.66 ± 1.79	32.13 ± 1.50
Surgical time (min)	146.13 ± 11.32	147.33 ± 9.50	146.07 ± 11.51	149.93 ± 10.50
Total Intraoperative IV fentanyl used (μg/kg)	18.06 ± 2.43	15.60 ± 2.84*	14.40 ± 2.02*	11.26 ± 1.38*, †

$P < 0.05$ is significant.
ACC: Aortic cross clamp time.
CPB: Cardiopulmonary bypass time.
* Significant when compared with control group.
† Significant when compared with ITF and ITF-Mg (0.5 mg) groups.

Table 3 Weaning off CPB parameters in the studied groups. Data are expressed in mean ± SD, number (percentage).

	Control group (n = 20)	ITF group (n = 20)	ITF-Mg (0.5 mg) group (n = 20)	ITF-Mg (1 mg) group (n = 20)
Spontaneous recovery of heart	19 (95%)	18 (90%)	18 (90%)	19 (95%)
DC shock	1 (5%)	2 (10%)	2 (10%)	1 (5%)
Dopamine use	7 (35%)	6 (30%)	6 (30%)	8 (40%)
Dopamine dose (μg/kg/min)	5 ± 1.9	6 ± 1.2	5 ± 1.6	5 ± 2
Nitro-glycerin use	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)
Nitroglycerine dose (μg/kg/min)	2.76 ± 1.29	2.83 ± 1.33	2.66 ± 1.34	2.80 ± 1.26

Table 4 Postoperative variables in the studied groups. Mean ± SD, number (%).

	Control group (n = 20)	ITF group (n = 20)	ITF-Mg (0.5 mg) group (n = 20)	ITF-Mg (1 mg) group (n = 20)
O.R. extubation	0	0	3 (15%)	6 (30%) [#]
Extubation time (h)	4.80 ± 1.43	4.10 ± .84	3.69 ± 1.18	1.84 ± 0.57[#]
Time to 1st analgesic requirement (h)	2.86 ± 1.64	7.30 ± 2.02[*]	8.42 ± 2.04[*]	10.33 ± 5.36[* †]
Postoperative fentanyl consumption μg/kg/24 h	7.06 ± 2.31	4.93 ± 2.37[*]	4.66 ± 2.09[*]	3.76 ± .97[*]
ICU length of stay (h)	32.60 ± 3.26	31.80 ± 3.50	30.60 ± 3.54	30.33 ± 3.99
hospital length of stay (days)	6.13 ± .63	5.80 ± .67	5.80 ± .67	5.80 ± .67
Nausea and Vomiting	2 (10%)	2 (10%)	1 (5%)	1(5%)
Pruritus	0	0	0	0
Neurologic deficit	0	0	0	0
Bromage score	I	I	I	I

$P < 0.05$ is significant.
[*] Significant when compared with control.
[†] Significant when compared with ITF and ITF-Mg (0.5 mg) groups.
[#] Significant when compared with control and ITF groups.

ITF-Mg (0.5 mg) (Table 4). As regard to postoperative fentanyl consumption μg/kg/24 h, it was more in the control group as compared with other groups (4.93 ± 2.37 in ITF, 4.66 ± 2.09 in ITF-Mg (0.5 mg), 3.76 ± .97 in ITF-Mg (1 mg), and 7.06 ± 2.31 in control group There were no significant differences between the four groups as regards ICU and hospital length of stay. There were no significant differences between the four groups as regard to postoperative Bromage score and adverse effects as nausea and vomiting, pruritus, and neurologic deficit (Table 4).

Table 5 shows laboratory evaluation of the stress response (serum cortisol and blood glucose) and serum magnesium. There were no significant differences between the four groups in serum cortisol and blood glucose at different stages of evaluation, but there were significantly high serum cortisol and blood glucose at 1 h after termination of CPB when compared with their basal values in the four groups (Table 5). There were no significant differences between preoperative and postoperative serum magnesium levels (Table 5).

In this study, postoperative objective pain discomfort score was significantly lower in the ITF-Mg (1 mg) group in the early postoperative period when compared with the other groups (Table 6).

In the current study, the mean arterial blood pressure (Table 7) and heart rate (Table 8) were significantly lower in the ITF-Mg (1 mg) group intraoperatively and early postoperatively when compared with the other groups. Also, there were no significant differences between the four groups as regards the perioperative central venous pressure, SaO_2, PaO_2 and $PaCO_2$.

4. Discussion

The results of this study demonstrated that the use of intrathecal fentanyl/magnesium (1 mg/kg) in pediatric patients subjected to elective open cardiac surgery provided superior hemodynamic stability, reduced intra and postoperative analgesic consumption, prolonged the time to first analgesic

Table 5 Laboratory evaluation [serum cortisol (μg/dl), blood glucose (mg/dl), serum Mg^{+2} (mg/dl)]. Data are expressed in Mean ± SD.

	Control group (n = 20)	ITF group (n = 20)	ITF-Mg (0.5 mg) group (n = 20)	ITF-Mg (1 mg) group (n = 20)
Serum cortisol (μg/dl)				
Basal	14.82 ± 3.18	15.14 ± 5.33	15.20 ± 4.07	15.52 ± 4.18
Post sternotomy	15.22 ± 4.52	17.76 ± 4.56	15.35 ± 4.13	14.45 ± 4.78
1 h post CPB	59.28 ± 16.60[*]	57.08 ± 13.78[*]	60.92 ± 9.74[*]	61.78 ± 6.41[*]
24 h postoperative	16.41 ± 8.11	17.27 ± 7.00	18.12 ± 6.42	17.82 ± 3.75
Blood glucose (mg/dl)				
Basal	79.26 ± 5.03	79.40 ± 5.74	79.60 ± 5.48	78.26 ± 5.92
Post sternotomy	117.33 ± 6.94	115.13 ± 6.34	111.47 ± 5.76	110.80 ± 6.48
1 h post CPB	206.13 ± 11.89[*]	213.27 ± 12.63[*]	207.40 ± 14.48[*]	202.13 ± 27.86[*]
24 h postoperative	81.86 ± 5.40	82.33 ± 5.82	80.40 ± 5.35	79.86 ± 5.33
Serum Mg^{+2} (mg/dl)				
Preoperative	1.50 ± .58	1.34 ± .42	1.36 ± .48	1.47 ± .48
Postoperative	1.43 ± .53	1.31 ± .36	1.27 ± .46	1.40 ± .37

$P < 0.05$ is significant.
[*] Significant when compared with their basal value.

Table 6 Postoperative pain score in the studied groups. Data are expressed in median (range).

	Control group (n = 20)	ITF group (n = 20)	ITF-Mg (0.5 mg) group (n = 20)	ITF-Mg (1 mg) group (n = 20)
After 1 h	5(3–7)	5(3–8)	5(3–7)	2(0–5)*
After 2 h	4(3–6)	4(3–6)	4(3–5)	2(0–4)*
After 3 h	4(3–6)	4(1–5)	4(1–5)	2(0–4)*
After 4 h	4(2–5)	4(1–5)	3(1–5)	1(1–4)*
After 5 h	4(2–5)	4(1–5)	3(1–4)	2(1–3)*
After 6 h	4(2–5)	3(0–5)	3(0–5)	2(1-3)*
After 7 h	4(2–5)	3(1–4)	3(1–4)	1(0-3)*
After 8 h	3(2–5)	3(1–5)	3(2–4)	2(0–3)*
After 9 h	3(2–4)	3(0–5)	3(1–5)	1(0–3)*
After 10 h	3(2–5)	3(0–5)	2(0–4)	1(0–2)*
After 11 h	3(2–4)	3(0–4)	2(0–4)	1(0–2)*
After 12 h	3(2–4)	3(0–4)	2(0–4)	1(0-2)*

$P < 0.05$ is significant
* Significant when compared with control, ITF and ITF-Mg (0.5 mg) groups.

Table 7 Perioperative MAP (mmHg) in the studied groups. Data are expressed in mean ± SD.

	Control group (n = 20)	ITF group (n = 20)	ITF-Mg (0.5 mg) group (n = 20)	ITF-Mg (1 mg) group (n = 20)
Basal	70.80 ± 5.15	71.46 ± 4.54	70.66 ± 4.83	70.33 ± 3.26
Intraoperative				
Post induction	81.86 ± 5.01	80.73 ± 6.95	79.73 ± 5.04	82.00 ± 5.00
After skin incision	80.46 ± 5.39	78.00 ± 5.95	79.13 ± 5.16	75.20 ± 4.27*
Post sternotomy	82.46 ± 4.38	77.66 ± 5.36	78.66 ± 4.13	72.93 ± 3.76*
30 min post CPB	81.33 ± 4.32	77.73 ± 5.89	76.20 ± 5.89	70.80 ± 4.76*
60 min post CPB	83.00 ± 5.05	76.86 ± 6.41	77.13 ± 5.15	72.00 ± 5.87*
Postoperative				
After 1 h	82.86 ± 5.11	78.86 ± 6.77	77.73 ± 4.81	71.80 ± 5.47*
After 6 h	80.66 ± 6.60	79.00 ± 6.67	78.40 ± 5.09	74.20 ± 5.93*
After 12 h	79.33 ± 6.44	79.86 ± 5.97	79.86 ± 5.48	75.06 ± 5.61

$P < 0.05$ is significant.
* Significant when compared with control group.

Table 8 Perioperative HR (beats/min) in the studied groups. Data are expressed in mean ± SD.

	Control group (n = 20)	ITF group (n = 20)	ITF-Mg (0.5 mg) group (n = 20)	ITF-Mg (1 mg) group (n = 20)
Basal	106 ± 5	105 ± 8	106 ± 7	106 ± 6
Intraoperative				
Post induction	115 ± 4	113 ± 6	115 ± 4	109 ± 22
After skin incision	119 ± 26	117 ± 8	119 ± 7	115 ± 5
Post sternotomy	122 ± 4	118 ± 7	117 ± 6	111 ± 4*
30 min post CPB	126 ± 7	120 ± 7	116 ± 8	113 ± 6*
60 min post CPB	129 ± 5	121 ± 6	120 ± 9	115 ± 8*
Postoperative				
After 1 h	128 ± 10	120 ± 7	121 ± 9	114 ± 7*
After 6 h	125 ± 8	121 ± 6	119 ± 11	114 ± 7*
After 12 h	125 ± 7	121 ± 6	121 ± 6	119 ± 8

$P < 0.05$ is significant.
* Significant when compared with control.

request and allowed early tracheal extubation when compared with intravenous fentanyl, intrathecal fentanyl or intrathecal fentanyl/magnesium (0.5 mg/kg) but did not affect the stress response to CPB.

In this study, the analgesic profile was better with ITF, ITF-Mg 0.05 mg/kg and ITF-Mg 1 mg/kg groups than the control group in pediatric patients undergoing cardiac surgery. As these groups were associated with less total intraoperative i.v. fentanyl used, less postoperative analgesic requirements (Postoperative fentanyl consumption μg/kg/24 h) and prolonged time to 1st analgesic requirement when compared with the control group. More specifically, intraoperative fentanyl

used in ITF-Mg (1 mg) was statistically less as compared with ITF and ITF-Mg (0.5 mg) groups. Also, time to 1st analgesic requirement is prolonged in ITF-Mg (1 mg)/group as compared with ITF and ITF-Mg 0.05 mg/kg groups. This is in accordance with earlier clinical human investigations, which reported increased duration of analgesia with intrathecal magnesium in various obstetric and non-obstetric populations [9,13]. Also, another study found that the addition of $MgSO_4$ to spinal anesthesia prolonged the time to first analgesic requirement, but did not reduce total analgesic consumption in the first 24 h [10].

In another study, Pirat et al. [15] compared cardiovascular and neurohumoral responses associated with I.T. fentanyl (2 μg/kg) in first group, i.v. (10 μg/kg followed by an i.v. infusion of 10 μg/kg/h) in second group, and third group using a combination of both regimens in pediatric patients undergoing cardiac surgery. They found that patients receiving a combination of both i.v. and IT fentanyl had less hemodynamic response to sternotomy than in either of the other groups. This study showed that the three groups (IV, IT, combined IV + IT) required approximately similar amounts of additional fentanyl during the operation, also there were no significant differences among the groups with respect to postoperative analgesic requirement. This study may confirm the advantage of adding Magnesium IT to fentanyl, and its analgesic effect based on our analgesic profile in pediatric patients subjected to cardiac surgery.

In the current study, all patients in the four groups were extubated early (less than 6 h), however, the number of patients who were extubated in the operating room was, significant more in the ITF-Mg (1 mg) group than other groups. This may be attributed to less intraoperative fentanyl used in this group, and hence less central respiratory depressant effect as explained by other studies [16]. The time to extubation was shorter in the ITF-Mg (1 mg) group than other groups and, also this may be explained by the decrease in the total intraoperative intravenous fentanyl used in these groups (18.06 ± 2.43 μg/kg in the control group, 15.60 ± 2.84 μg/kg in ITF group, 14.40 ± 2.02 μg/kg in ITF-Mg 0.5 mg/kg group and 11.26 ± 1.38 μg/kg in ITF-Mg 1 mg/kg group).

In contrast, Pirat et al. [15] cannot explain the significantly shorter extubation times in pediatric cardiac surgery that were recorded for Group IT + i.v., although using high dose of intravenous fentanyl (49.7 ± 6.1 μg/kg). However, this may be explained by short duration of action of fentanyl, strong tendency of fentanyl to bind to the surfaces of the CPB circuit, hemodilution and drug sequestration, which further decrease the plasma concentration of fentanyl.

Also, Davis et al. [17] defined intraoperative variables predictive of early extubation, as CPB time, aortic cross clamp time (ACC) and circulatory arrest time. These variables were of short time in our study, and hence enabled short extubation time in our study as compared with other studies with prolonged CPB, ACC, and circulatory arrest time.

The present study showed no significant differences as regards ICU and hospital length of stay. We found no significant hemodynamic effect (hypotension) following the addition of magnesium to our spinal solution and addition of intrathecal magnesium to fentanyl provides hemodynamic stability. This may be attributed to the absence of systemic vasodilator effects of spinal magnesium in this dose and this was shown in normal Mg^{+2} serum level in the postoperative values.

As regards the stress response to cardiac surgery, we used serum cortisol and blood glucose as hormonal and metabolic indicators of the stress response. The four groups showed significantly higher serum cortisol and blood glucose levels at one hour after CPB when compared with the basal values. These findings concur with the results of another study [15] and are believed to be related to several factors as, systemic inflammatory response, hypotension, and hypothermia associated with CPB, independent of the used opioid dose. These results indicated that the above four mentioned anesthetic regimens were not enough to blunt stress response.

Considering respiratory depression, pruritus, nausea and vomiting all of which are well recognized adverse effects of spinal opioid usage. There were no reported cases as regard to incidence of respiratory depression in all studied groups (as the postoperative arterial blood gases showed neither significant hypoxemia nor hypercapnia in the 4 groups). As regard to nausea and vomiting, it was minimal self limiting problem, and didn't require treatment.

This may be explained by the pharmacokinetics of fentanyl, which is a lipid-soluble opioid, binds fairly rapidly with the opioid receptors in the dorsal horn of the spinal cord leaving only small amounts of substance for cephalad migration to the fourth ventricle, and chemoreceptor trigger zone, in contrast with the less lipid-soluble morphine [18].

This is in accordance with the result of Pirate et al. [15] who found no problems with these adverse effects on similar group of patients although using larger doses of fentanyl both intrathecal and intravenous.

Varassi et al. [19] reported that the subarachnoid administration of 25 μg of fentanyl during spinal anesthesia in non-premedicated men did not cause early respiratory depression in elderly patients. An increased risk of respiratory depression in laboring parturient has been reported with systemic $MgSO_4$ therapy [20]. An increased incidence of respiratory depression may be expected when these two drugs are neuroaxially combined; however, we did not observe this in this study, and this in accordance with other studies that investigate neuroaxial magnesium [9,10,13], all of these studies proved that absence of respiratory depressant effect of neuroaxial magnesium.

Urinary retention is another side effect of intrathecal opioids, we recorded no cases of urinary retention because all patients had a urinary catheter in place inserted before surgery, remained in place in the ICU. However, no reported retention was recorded after the catheter removal.

In this study, there was no neurological deficit, or signs suggestive of epidural hematoma, nerve compression or neurotoxicity even on long term follow up (up to 2 months), the absence of epidural hematoma may be due to use of a 25-gauge spinal needle inserted at L3–4 or L4–5 approximately one hour before administration of heparin and this coincides with another studies [15,17,21].

The current study showed no significant differences between the studied groups in the criteria of weaning off CPB as regards the spontaneous recovery of the heart, the need for DC shocks for defibrillation and the need for inotropes or vasodilators. This may be explained by other studies that reported that myocardial injury in pediatric cardiac surgery in infants and children was dependent on age and ischemic time and type of surgical procedure [22]. Also previous ventricular function determines the need for inotropic support during weaning off CPB [23]. Since that the age, type of surgical

procedure and aortic cross clamp time were nearly the same in the four studied groups, there were no significant differences in the weaning parameters between the studied groups. Thus, this study indicated that weaning off CPB was not affected by intrathecal fentanyl or intrathecal fentanyl-magnesium.

The present study showed that heart rate and mean arterial blood pressure both intra and post operatively were significantly lower in intrathecal fentanyl-magnesium 1 mg/kg group than the control group. The explanation for this is that spinal opioids may only attenuate increased sympathetic nerve activity elicited by myocardial ischemia in patients undergoing cardiac surgery [24] and addition of magnesium had synergistic effects to spinal opioid in this dosage.

The current study indicates that preoperative administration of intrathecal fentanyl-magnesium 1 mg/kg in pediatric patients submitted to open heart surgery for congenital heart repair provided lower pain scores in the early postoperative period with subsequent lower dosages of fentanyl consumed postoperatively when compared with the control group. Because no published study has assessed the effectiveness of intrathecally injected $MgSO_4$ in preventing postoperative pain in pediatric cardiac surgery, no reported data are available for comparison.

In conclusion, the use of intrathecal fentanyl-magnesium (1 mg/kg) in pediatric patients subjected to open cardiac surgery provided superior hemodynamic stability, reduced intra and postoperative analgesic consumption, prolong the time to first analgesic request and allows early tracheal extubation when compared with intravenous fentanyl, intrathecal fentanyl or intrathecal fentanyl-magnesium (0.5 mg/kg).

Further studies are recommended in which different doses of magnesium are to be used, including a large number of patients, and long term follow up for subsequent years. The absence of any adverse hemodynamic effects or prolonged respiratory depression after IT fentanyl-magnesium administration is encouraging and suggests that further studies involving larger doses of IT fentanyl-magnesium may be of value. Despite the promise that IT administration may offer, the potential benefits of such an invasive procedure must always be weighed against the potential risks.

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