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ORIGINAL ARTICLE

Does the addition of magnesium to bupivacaine improve postoperative analgesia of ultrasound-guided thoracic paravertebral block in patients undergoing thoracic surgery?

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Abstract
Purpose Magnesium is a plentiful intracellular cation that has been reported to possess analgesic effect. The present study was aimed to see whether addition of magnesium to bupivacaine in thoracic paravertebral block (TPVB) improved the analgesic effect after thoracic surgery.
Materials and methods Fifty adult patients undergoing elective open thoracic surgery were divided into two equal groups. Group I received 12 ml of 0.5 % bupivacaine plus 0.9 % saline (3 ml) whereas Group II received 12 ml of 0.5 % bupivacaine plus 150 mg magnesium sulphate (in 3 ml 0.9 % saline) for TPVB. The following parameters were assessed: onset, dermatomal levels and duration of sensory block, duration of analgesia, visual analogue scale (VAS) for pain, postoperative intravenous morphine consumption, pulmonary function tests (peak expiratory flow rate [PEFR], forced expiratory volume in 1 s [FEV1] and forced vital capacity [FVC]) before and 24 h after surgery, and complications from the drugs and technique.
Results Group II patients showed a significantly longer sensory block duration (224.6 ± 59.3 vs 160.1 ± 55.2 min, $P < 0.05$), longer duration of analgesia (388.8 ± 70.6 vs 222.2 ± 61.6 min, $P < 0.05$), less VAS during the postoperative 48 h, less need for postoperative morphine (16.2 ± 7.4 vs 29.5 ± 11.1 mg, $P < 0.05$) and lower incidence of somnolence (0 [0 %] vs 5 [20 %], $P < 0.05$). Furthermore, postoperative pulmonary function tests (PEFR, FEV1 and FVC) were significantly better in Group II whereas there was no significant difference between both groups regarding the sensory block dermatomal level or hemodynamic data.
Conclusion Addition of magnesium to bupivacaine in TPVB improved the analgesic effect of bupivacaine in patients undergoing thoracic surgery.

Keywords Analgesia · Bupivacaine · Magnesium · Thoracic paravertebral block

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Introduction

Thoracic paravertebral blockade (TPVB) is performed for postoperative analgesia in patients undergoing unilateral breast, thoracic or upper abdominal surgeries. The local anesthetic is injected into the thoracic paravertebral space which is a wedge-shaped space on either side of the vertebral column [1]. In contrast to thoracic epidural analgesia, TPVB provides unilateral analgesia and sympathetic block resulting in less effect on patient's hemodynamics [2]. The use of ultrasound increases the ability to view the boundaries of the thoracic paravertebral space [3].

Magnesium has a role in various physiological processes that include transmembrane ion flux, control of calcium channels gating, heart excitability, vascular tone, neuronal activity and neurotransmitter release [4]. Many animal and human studies have reported safety and efficacy of adding magnesium to local anesthetics in various regional anesthetic procedures, such as intrathecal, epidural, caudal, brachial plexus blocks and intravenous regional anesthesia (IVRA), yet other investigations have shown reduced or negative analgesic effects when using magnesium [5–8]. Various adjuvants and drug regimes for TPVB have been investigated for analgesia after thoracotomy [9]. However,

so far, there is no consensus on the best adjuvants or drug regimes for TPVB.

The aim of this study is to test the hypothesis that addition of magnesium to bupivacaine in TPVB may improve postoperative analgesic efficacy.

Materials and methods

The current study was carried out after a written informed consent was obtained from all patients and institutional review board approval was obtained. Fifty adult patients undergoing elective open thoracic surgery were included in the study. Patients were excluded from the study if they had cardiac problem, significant obstructive or restrictive lung diseases (vital capacity or forced expiratory volume in 1 s [FEV1] <50 % of the predicted values), pulmonary hypertension (mean pulmonary artery pressure >30 mm Hg), preexisting coagulation disorders, refusal of the patients to give informed consent, morbid obesity (body mass index $\geq$ 30), spinal deformity and local infection at the site of the block. Preoperative evaluation of the patients was done by complete history taking, thorough clinical examination, chest X-ray, pulmonary function tests, arterial blood gases analysis, ECG and echocardiography. The patients were instructed preoperatively in the use of the 100-mm linear visual analogue scale (VAS) for pain assessment (0 mm = no pain and 100 mm = worst pain imaginable). Furthermore, the use of the hand-held spirometer (Vitalograph, Milton Keynes, UK) was instructed to the patients and preoperative baseline peak expiratory flow rate (PEFR), FEV_1 and forced vital capacity (FVC) were recorded. The patients were randomly allocated preoperatively to receive TPVB using bupivacaine (Group I, $n = 25$) or bupivacaine plus magnesium (Group II, $n = 25$) using a random number table. An independent statistician was assigned to perform central randomization to ensure proper concealment of the study management from the patients and investigators until the release of the final statistical results.

A single-injection ultrasound guided TPVB was performed by the attending anesthesiologist in all patients in the lateral position before induction of general anesthesia using a 38 mm broadband linear array ultrasound probe (5–10 MHz of a Hewlett-Packard 77020A ultrasound monitor [Andover, MA]). The patients were continuously monitored during the technique and thereafter (continuous ECG, pulse oximetry, capnography, noninvasive blood pressure). The patients were given 1–2 mg of midazolam i.v. and 50–100 μg of fentanyl i.v. just before introducing the needle. Four ml of 1 % lidocaine was injected subcutaneously at the puncture site. A sagittal paramedian view of the paravertebral space was obtained by applying the probe at a point 2.5 cm lateral to the tip of the spinous process in a vertical orientation. The fifth thoracic vertebral level was identified by palpating and counting down from the seventh cervical body. The midpoint of the transducer was aligned midway between the transverse processes of T5 and T6 and 22G spinal needle was inserted in an in plane approach in a cephalad orientation and was advanced perpendicularly to all skin planes under direct vision to puncture the superior costotransverse ligament where a click may be appreciated. The local anesthetic solution was then injected between the superior costotransverse ligament and the parietal pleura which was displaced anteriorly by the injectate. The injectate was 12 ml of 0.5 % bupivacaine plus 0.9 % saline (3 ml) in Group I or 12 ml of 0.5 % bupivacaine plus 150 mg magnesium sulphate (in 3 ml 0.9 % saline) in Group II. The mean pH of the injectate was 5.8 in both groups. Sensory block over the area of surgical incision was confirmed by loss of cold sensation using an alcohol swab and pinprick sensation using a 23 G needle every 3 min until 20 min after injection of the study solutions and before starting general anesthesia (Sensory block onset was defined when the patient subjectively evaluated the intensities of both cold and pinprick sensations in the blocked side decreased 75 % or more compared with the contralateral [non-blocked] side as a reference). General anesthesia was induced with propofol 1.5–2 mg/kg and fentanyl 3 μg/kg. Tracheal intubation was facilitated by administration of cis-atracurium 0.1 mg/kg. Anesthesia was maintained with isoflurane 1MAC and cis-atracurium 2 μg/kg/min. A left-sided double-lumen endobronchial tube (DLT, Mallinckrodt's Broncho-Cath 39 or 41 Fr, Mallinckrodt Medical Ltd, Athlone, Ireland) was inserted and a fiberoptic bronchoscope was used to confirm proper position of the tube. The patients were ventilated with a tidal volume of 10 ml/kg and the respiratory rate was adjusted to keep the end-tidal CO_2 between 35 and 45 mmHg. The patients were monitored by continuous electrocardiogram, invasive blood pressure, central venous pressure, pulse oximetry and capnography. All operations were performed by the same surgical team and using the same techniques. After surgery, the patients were monitored in the ICU for at least 24 h and were given supplementary oxygen 2–3 l/min via nasal cannulae for the first 24 h to maintain oxygen saturation greater than 92 %. Fluids and blood transfusions were given as needed to keep central venous pressure $\geq$4 cm H_2O, urine output $\geq$1 ml/kg/h, and hemoglobin level $\geq$10 g/dl. All patients were given acetaminophen 1 g i.v. every 6 h during first 24 h after surgery, then acetaminophen 1 g was given orally every 6 h for 4 days. A bolus of intravenous morphine 0.1 mg/kg was administered with a minimum interval of 15 min if the patient requested or the VAS for pain at rest was more than 30 mm. Ondansetron

4 mg i.v. was administered in case of reported nausea and or vomiting. Both the patients and the observer who recorded the postoperative data were blinded to the group assignment.

The following parameters were recorded: (i) Sensory block onset. (ii) Upper and lower dermatomal level of sensory blockade (assessed every 3 min until 20 min after injection of the study solutions). (iii) Sensory block duration (time from injection of the local anesthetic to complete recovery of cold and pain sensation as tested by alcohol swab and pinprick sensation. (iv) Duration of analgesia (time interval from block placement till first need of intravenous morphine). (v) Pain scoring: VAS at rest and during coughing at 1, 2, 3, 12, 24, 36 and 48 h postoperatively. (vi) The amount of i.v. morphine consumed during the postoperative 48 h. (vii) SaO_2, $PaCO_2$, HR and MAP recorded before TPVB, at 30 min. after TPVB, end of surgery and 2 h after surgery. (viii) Pulmonary function tests (PEFR, FEV_1 and FVC) recorded before and 24 h after surgery. (ix) Complications from the drugs and technique (local anesthetic toxicity, nausea, vomiting, pneumothorax, hypotension, bradycardia). The primary outcome measure was duration of analgesia. Secondary outcome measures were sensory block onset, duration and dermatomal level, pain scoring, opioid requirements, arterial blood gases, pulmonary functions, hemodynamics and any suspected adverse drug reactions.

Prior to the study, a power analysis was performed to determine the necessary number of patients in each group based on duration of analgesia and a preliminary study that had demonstrated that the mean value of analgesia duration was 230 ± 70 min for patients scheduled for TPVB using bupivacaine for thoracotomy in our hospital. With a 2-sided type I error of 5 % and study power at 80 %, it was estimated that 22 patients would be needed in each group in order to detect a difference of 80 min in the duration of analgesia between the two groups. We preferred to study 25 patients in each group in order to decrease the chance of insufficient power, in case the observed variability was higher than expected. Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range) and categorical variables are reported as numbers (percentages). Statistical analysis was done by using Statistica version 6 (StatSoft Inc.; Tulsa, OK) and GraphPad Prism version 4 (GraphPad Software Inc.; San Diego, CA) software. Student's unpaired *t* test was used to compare normally distributed continuous variables (demographic and operative data, sensory block onset and duration, duration of analgesia and morphine needed over 48 h) and Mann–Whitney *U* test was used for comparison of non parametric data (sensory block levels and VAS). Cardiopulmonary variables were analyzed using two-way analysis of variance (ANOVA) for repeated measures. This was followed by Student–Newman–Keuls test, if a difference between groups had been detected. Categorical variables were compared by chi-square test or Fisher's exact test, as appropriate. All analyses were two-tailed and $P < 0.05$ was considered statistically significant.

Results

Both groups were comparable in the demographic and operative data as shown in Table 1. Successful block was achieved in all patients and was comparable in both groups regarding upper and lower dermatomal levels (Table 2) and no cases of respiratory depression (low oxygen saturation, low respiratory rate or apnea) were reported. Group II showed a significantly longer sensory block duration, longer duration of analgesia, less need for postoperative morphine and less incidence of somnolence (Table 2). The incidences of nausea and vomiting, pruritus and dizziness were not different between the groups (Table 2). The time course of VAS score after surgery at rest and at coughing is shown in Figs. 1 and 2, respectively, and demonstrated statistically significant less pain in Group II at 1, 2, 3, 12,

Table 1 Demographic and operative data of the patients receiving bupivacaine or bupivacaine + magnesium for thoracic paravertebral block

Variable	Group I (bupivacaine) ($N = 25$)	Group II (bupivacaine + magnesium) ($N = 25$)	*P* value
Age (years)	48.4 ± 11.0	49.4 ± 12.2	0.76
Sex (M/F)	17/8	16/9	0.54
Weight (kg)	75 ± 8.4	76 ± 7.9	0.88
Height (cm)	170 ± 13	171 ± 12	0.83
Operative time (min)	134 ± 44	136 ± 47	0.79
Types of surgery			
Lobectomy	8	7	0.75
Wedge resection	16	17	0.76
Pneumonectomy	1	1	N/A
Anesthesia time (min)	145 ± 46	147 ± 50	0.66

Data are given as mean ± SD or numbers. *N/A* non applicable

Table 2 Characters of the paravertebral block and postoperative pain in both groups

Variable	Group I (bupivacaine) ($N = 25$)	Group II (bupivacaine + magnesium) ($N = 25$)	P Value
Onset of sensory block (min)	14.3 ± 3.2	12.5 ± 2.9	0.45
Upper sensory level (thoracic dermatome)	3 (1.9–4.2)	2.9 (1.7–4.1)	0.76
Lower sensory level (thoracic dermatome)	7.9 (6.3–10.3)	8.1 (6.5–10.4)	0.69
Sensory block duration (min)	160.1 ± 55.2	224.6 ± 59.3	0.01*
Duration of analgesia (min)	222.2 ± 61.6	388.8 ± 70.6	0.001*
Morphine(mg) needed over 48 h	29.5 ± 11.1	16.2 ± 7.4	0.01*
Side effects			
Nausea and vomiting	5 (20 %)	3 (12)	0.35
Pruritus	2 (8 %)	1 (4 %)	0.50
Dizziness	4 (16 %)	0 (0 %)	0.05
Somnolence	5 (20 %)	0 (0 %)	0.03*

Data are expressed as mean ± SD, median (interquartile range) or number (%). * indicates significant difference between both groups ($P < 0.05$)

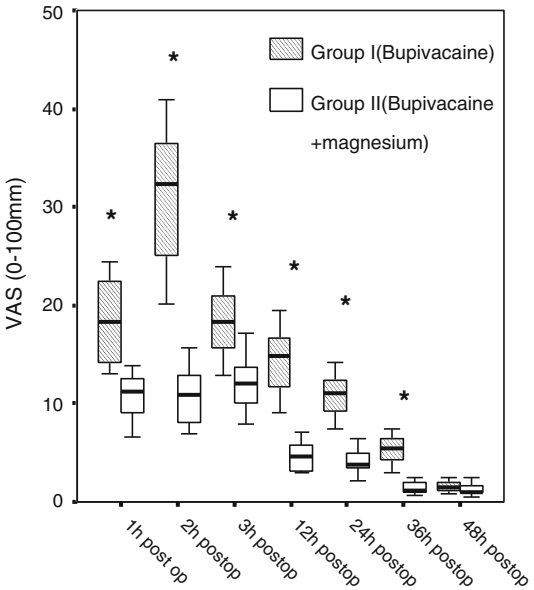

Fig. 1 Visual analogue scale during rest over the first 48 postoperative hours. Data are expressed as median (range). *Indicates significant difference between both groups ($P < 0.05$)

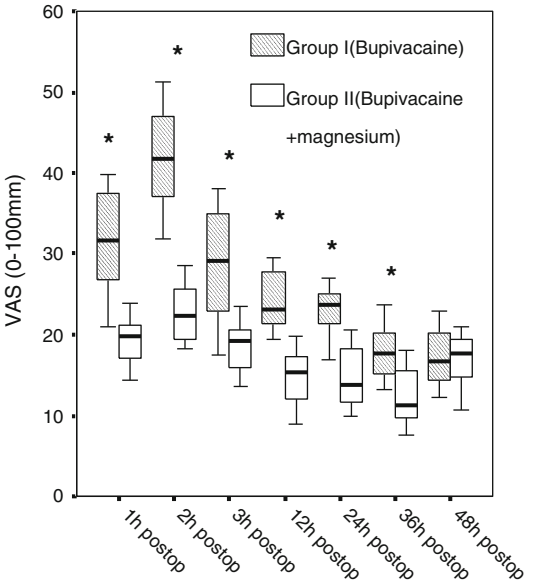

Fig. 2 Visual analogue scale during coughing over the first 48 postoperative hours. Data are expressed as median (range). *Indicates significant difference between both groups ($P < 0.05$)

24 and 36 h postoperatively ($P < 0.05$, Mann–Whitney U test). Furthermore, postoperative pulmonary function tests (PEFR, FEV_1 and FVC) were significantly better in Group II ($P < 0.05$) and there was no significant difference between both groups regarding the hemodynamic data (Table 3). No complications were recorded related to the technique performed.

Discussion

The present study showed that addition of magnesium to bupivacaine for TPVB provided longer duration of analgesia, less VAS during postoperative 48 h, less need for postoperative morphine and lower incidence of somnolence. Furthermore, postoperative pulmonary function tests (PEFR, FEV_1 and FVC) were significantly better in the magnesium group (Group II). Our results confirm the findings of previous studies showing that addition of magnesium to local anesthetics improved the efficacy and quality of various regional anesthetic procedures, such as intrathecal, epidural, caudal, brachial plexus blocks and intravenous regional anesthesia (IVRA) [5–7].

In a clinical study in parturiants requesting labor analgesia, intrathecal magnesium sulphate ($MgSO_4$) 50 mg increased the duration of spinal opioid analgesia without additional side effects [6]. Similar findings about analgesic effect of intrathecal $MgSO_4$ were shown in other studies that reported increase in the duration of opioid analgesia by the use of $MgSO_4$ [10, 11]. The safety of intrathecal

Table 3 Cardiopulmonary variables in the 2 groups

Variable	Group I (bupivacaine) ($N = 25$)	Group II (bupivacaine + magnesium) ($N = 25$)	P Value
HR (b/m)			
Before TPVB	78.1 ± 11.3	79.2 ± 12.2	0.69
30 min after TPVB	76.1 ± 10.8	77.01 ± 10.5	0.71
End of surgery	74.3 ± 10.0	73.9 ± 11.03	0.62
2 h after surgery	73.4 ± 11.5	72.1 ± 10.8	0.68
MAP (mmHg)			
Before TPVB	88.6 ±10.2	89.1 ± 11.1	0.71
30 min after TPVB	87.8 ± 10.5	88.4 ± 10.5	0.73
End of surgery	87.9 ± 11.1	87.8 ± 10.8	0.70
2 h after surgery	84.6 ± 10.1	85.3 ± 10.6	0.69
SaO_2 (%)			
Before TPVB	97 ± 1	97 ± 1	0.91
30 min after TPVB	98 ± 2	97 ± 2	0.94
End of surgery	98 ± 1	98 ± 1	0.96
2 h after surgery	97 ± 1	98 ± 2	0.99
$PaCO_2$ (mm Hg)			
Before TPVB	40 ± 6	39 ± 5	0.83
30 min after TPVB	39 ± 4	39 ± 5	0.91
End of surgery	39 ± 5	40 ± 4	0.99
2 h after surgery	40 ± 6	40 ± 5	0.92
PEFR (% predicted)			
Before surgery	80.3 ± 20.2	82.0 ± 18.72	0.97
24 h after surgery	42.1 ± 15.7	59.8 ± 16.3	0.01*
FEV1 (% predicted)			
Before surgery	77.1 ± 16.2	78.6 ± 14.9	0.99
24 h after surgery	33.3 ± 15.4	53.1 ± 14.6	0.002*
FVC (% predicted)			
Before surgery	70.1 ± 13.2	73.5 ± 14.0	0.83
24 h after surgery	28.4 ± 10.5	39.9 ± 11.1	0.01*

HR heart rate, *MAP* mean arterial pressure, SaO_2 arterial oxygen saturation, $PaCO_2$ arterial carbon dioxide tension, *PEFR* peak expiratory flow rate, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity. Data are expressed as mean ± SD. *indicates significant difference between both groups ($P < 0.05$)

$MgSO_4$ has been demonstrated in both animal and human models [11–13]. Intrathecal administration of 1.25 mg $MgSO_4$ in rats on alternate days over 30 days has provided transient sensory and motor block without any adverse outcomes. Furthermore, histological examination of the spinal cord did not show any abnormalities [12]. Different theories have been suggested to explain the antinociceptive effect of magnesium that include interference with calcium channels and noncompetitive blocking of *N*-methyl-D-aspartate receptors [14–17].

In a clinical study of epidural anesthesia [18], $MgSO_4$ was used epidurally in a dose of 50 mg in combination with bupivacaine for patients undergoing lower abdominal and lower limb surgeries. It accelerated onset of epidural anesthesia without any complications. Another study added 50 mg of $MgSO_4$ to 0.25 % ropivacaine for caudal analgesia in pediatrics and resulted in reduction in the anesthetic requirements [19]. An animal trial in cattle [20], reported that addition of 1 ml of 10 % $MgSO_4$ to caudal lidocaine resulted in a longer duration of analgesia (168 ± 2.6 vs 59.8 ± 3.4 min in the control). In another trial, addition of 150 mg $MgSO_4$ to prilocaine for axillary brachial plexus block resulted in longer sensory and motor block without any adverse effects [21]. We used the same dose of 150 mg $MgSO_4$ in our study which was effective and safe. In a recent study [7], addition of 2 ml of 10 % $MgSO_4$ to bupivacaine resulted in longer analgesia during interscalene nerve block. In another study [22], 6 ml of 25 % $MgSO_4$ was added to lidocaine for IVRA in upper limb surgery. It resulted in a more rapid onset of sensory and motor block and lowered tourniquet pain without any adverse effects.

It should be emphasized that in contrast to the previous trials, our study has evaluated the analgesic effect of magnesium by both subjective variables (VAS, duration of analgesia and morphine needed over 48 h) and objective variables (spirometric measurements) which gives major originalities to the current study. Augmentation of thoracic paravertebral bupivacaine by magnesium resulted in less

postoperative pain with consequent better postoperative pulmonary functions. However, few studies have evaluated spirometric measures as indicators of development of pulmonary dysfunction after thoracotomy and reported that pain is the most important factor responsible for the decrease in pulmonary function after thoracic surgery [23, 24]. Another emphasis is the fact that magnesium has a muscular relaxant effect which may lead to a negative impact on spirometric variables. However, postoperative spirometric measures in the current study suggest that the dose of magnesium used in this study had a positive effect on postoperative respiratory function. Furthermore, magnesium is known to have a vasodilator effect and negative inotropic, chronotropic and dromotropic effects on the heart which may result in undesirable effect on hemodynamics. The dose of magnesium used in this study did not cause any unfavorable effect on cardiovascular system.

In contradiction with our results, a study done by Birbicer et al. [8], found no difference in analgesia by adding 50 mg of magnesium to 0.25 % ropivacaine for caudal anesthesia in pediatrics. The mechanism of this contradictory finding is unclear but appears to be independent of the action of ropivacaine and $MgSO_4$ at the receptors within the Na+ channel but may be due to a relatively insufficient dose of $MgSO_4$ used in that study.

Our study has the limitation of only one dose–response assessment. In addition, we have not examined magnesium as a sole analgesic agent.

In conclusion, the findings of the present study supports the effective use of magnesium as an adjunct to local anesthetics for TPVB to improve and prolong the analgesia and spare need for intravenous opioids. All of these effects provide better postoperative pulmonary functions.

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