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Research Article

Effect of adding magnesium sulphate to bupivacaine on the clinical profile of ultrasound-guided thoracic paravertebral block in patients undergoing modified radical mastectomy

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KEYWORDS

Sonar-guided;
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Abstract *Background:* Paravertebral block is an effective perioperative analgesic modality in patients undergoing breast or thoracic surgery. Several adjuvants have been reported to improve the clinical profile of local anaesthetic-induced paravertebral block. In the present study, we hypothesized that the addition of magnesium sulphate could potentiate the analgesic effects of paravertebral bupivacaine in female patients undergoing modified radical mastectomy.

Methods: Ninety female patients ASA physical status 1 and 2 patients scheduled for modified radical mastectomy were allocated into 2 groups (45 patients each). Group (B) received bupivacaine 0.25% 0.3 ml/kg in the paravertebral space while group (BM) received 100 mg magnesium sulphate + bupivacaine 0.25% 0.3 ml/kg in the paravertebral space. Both blocks were done guided by ultrasound before induction of standard general anaesthetic technique which was the same in both groups. The two groups were assessed in the first post-operative 24 h for post-operative visual analogue scale (VAS) scores, time to first analgesic request, total 24 h morphine consumption, number of attacks of PONV and any complications from paravertebral block or from the drugs used in the study.

Results: Patients in group (BM) were found to have reduced VAS scores at 30 min, 2, 4, 6, 12, 24 h intervals post-operative. The time to first analgesic request was longer in patients of group (BM) with less amount of post-operative opioid consumption and consequently less number of attacks of PONV in first post-operative 24 h. These results were significant with a P value < 0.001.

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Conclusion: Adding magnesium sulphate to bupivacaine in ultrasound-guided paravertebral block resulted in more efficient analgesia and opioid-sparing in female patients undergoing modified radical mastectomy.

1. Introduction

Breast cancer surgery is the most common cancer surgery in women in the United States [1]. About 40% of breast cancer surgery patients complain from significant acute postoperative pain [2], and 50% of them develop chronic postoperative pain, commonly due to inadequate analgesia [3]. Breast surgery is frequently followed by postoperative nausea and vomiting (PONV), and restricted movement from pain [4]. One of the most promising techniques in providing better postoperative analgesia for breast cancer surgery patients is the paravertebral block (PVB) [5]. It is associated with better control of postoperative pain, less opioids requirement for postoperative analgesia, decrease in postoperative nausea and vomiting (PONV), reduced postoperative pulmonary complications and better patient outcome [5]. It was also reported that paravertebral block decreases chronic postoperative pain and improves wound subcutaneous oxygenation which leads to better wound healing and less risk of infection [6,7].

Several adjuvants as fentanyl and clonidine have been reported to improve the clinical profile of paravertebral block in breast surgery but addition of these adjuvants was associated with more adverse effects as hypotension and vomiting [8]. Paravertebral clonidine was also found to have a sedative effect [9]. Hence the need to try another adjuvant with better analgesic profile and with less adverse effects.

Magnesium is a competitive NMDA (N-methyl D-aspartate) receptors antagonist. NMDA receptors are excitatory amino acid receptors which are activated by various excitatory amino acid neurotransmitters such as glutamate and aspartate in response to painful stimuli. Activation of NMDA receptors leads to calcium influx into the cells, the action which can be blocked by magnesium [10]. Calcium influx leads to a series of central sensitization such as wind-up phenomenon and long term potentiation which are important mechanisms that determine the duration and intensity of post-operative pain, hence the role of magnesium as a NMDA receptors antagonist in the prevention of these cascades of reactions leading to reduced post-operative pain [11].

The mechanism of analgesic action of magnesium when injected in paravertebral space where the spinal nerves and posterior rami pass is still unclear. Theories about how magnesium exerts its action in paravertebral space may be systemic effect, epidural spread or direct action on the peripheral nerves. Systemic effect can be excluded as the dose of magnesium used in our study was a small dose and it was likely to be too low to produce a systemic effect or to pass through blood brain barrier. Also epidural spread is uncertain due to the absence of epidural side effects of local anaesthetic as hypotension. So the mechanism is likely the direct action of magnesium on the peripheral nerve by blocking the release of excitatory neurotransmitter at the synaptic junction or by potentiating the effect of local anaesthetic [12].

Magnesium has been used as an adjuvant to local anaesthetics in thoracic surgery and was found to improve analgesic efficacy [13]. The analgesic efficacy of magnesium in local anaesthetic-induced paravertebral block was not tried before in breast surgery.

We designed this study to evaluate the effect of magnesium sulphate as an adjuvant in potentiating the analgesic effect of bupivacaine in paravertebral block in breast cancer surgeries.

2. Patients and methods

After obtaining approval from the local Ethics Committee and written informed consent, 90 female ASA physical status 1 and 2 patients scheduled for modified radical mastectomy were enrolled in this study. This study was carried out at National Cancer Institute – Cairo University. The exclusion criteria were local infection at the site of the block, coagulation disorders, body mass index > 35, allergy to local anaesthetics or magnesium sulphate, patient refusal, severe respiratory or cardiac disorders, pre-existing neurological deficits, liver or renal insufficiency, pregnancy, breast reconstruction surgery, bilateral breast surgery, kyphoscoliosis, presence of acute herpes zoster, chronic pain syndrome, chronic analgesic use and psychiatric disease.

During the pre-anaesthetic assessment visit patients were educated about reporting pain on the 11-point visual analogue scale (VAS), where 0 = no pain and 10 = worst imaginable pain, and were also educated how to use the patient-controlled analgesia pump.

On arrival to the operating room, basic monitoring was initiated using non-invasive blood pressure measurements, continuous electrocardiography and pulse oximetry. Before induction of general anaesthesia, all patients received ultrasound-guided (US) thoracic paravertebral block (TPVB). The scanning probe was linear multi-frequency 13–16 MHz probe. The patients were sedated with midazolam 2 mg i.v. to relieve anxiety and provide comfort during the block. The patients were placed in the lateral position with the side of the surgery upwards. The site of paravertebral block was sterilized using iodine solution, and the ultrasound probe was covered by a disposable sterile cover.

After location of the paravertebral space by US, a 26-gauge needle was inserted 2.5 cm lateral to the cephalic edge of the fourth thoracic vertebral spinal process and skin and subcutaneous tissue were anaesthetized with 5 ml of lidocaine 20 mg/ml. High frequency linear ultrasound (U/S) probe was used to locate the paravertebral space and a 18 G Touhy needle was inserted perpendicular to hit the transverse process by an out-of-plane approach. After hitting this bony structure, the needle was redirected cephalic at 15° towards the paravertebral space. After localization of the needle in the paravertebral space and negative aspiration, injection of the medication prepared for each group of the study was

carried out. The correct placement of the injected drug was confirmed by expansion of the paravertebral space between the pleura and the superior costo-transverse ligament [14].

Patients were allocated to one of two groups of 45 patients each using a computer-generated random numbers concealed in sealed opaque envelopes. Group (B): received bupivacaine 0.25% 0.3 ml/kg in the paravertebral space. Group (BM): received 100 mg magnesium sulphate + bupivacaine 0.25% 0.3 ml/kg in the paravertebral space.

Success of the block was evaluated using the pinprick test within 30 min after the block. Failure of adequate paravertebral block was considered if evident loss of pinprick discrimination was delayed more than 30 min in dermatomes (T2–T6). Patients with failed block were excluded from the study. A staff anaesthesiologist not involved in the management of the patient or study prepared the paravertebral medication according to randomization. The patients and all staff involved in patient management and data collection were unaware of the group assignment.

General anaesthesia was induced using fentanyl 2 μg/kg i.v. and propofol 2 mg/kg and rocuronium 0.6 mg/kg to facilitate endotracheal intubation. Anaesthesia was maintained with sevoflurane with MAC 2–2.5%. Supplemental doses of rocuronium 0.1 mg/kg i.v. were administered as required to maintain muscle relaxation during surgery guided by peripheral nerve stimulator. The tidal volume was set at 8–10 ml/kg and respiratory frequency was adjusted to maintain end tidal CO_2 at 30 and 35 mmHg. Additional doses of fentanyl 1 μg/kg i.v. were given if heart rate and mean arterial blood pressure (MAP) increased more than 20% from the pre-operative baseline. Metoclopramide 10 mg i.v. was given 10 min before the end of the surgery. At the end of surgery, neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg and extubation was done after full return of consciousness.

After recovery from anaesthesia, the patients were transferred to the post-operative recovery room, and a patient controlled intravenous analgesia (PCA) device was ready to be connected on first request to postoperative analgesia. The PCA device was set to all groups with a demand dose of 1 mg morphine and a lockout interval of 10 min and without a continuous background infusion [15].

All patients were assessed for the following parameters:

Pain: Visual analogue scale (VAS) score was used to assess the pain scores in the patient by a blinded observer both at rest and on movement of the shoulder at 30 min and subsequently 2, 4, 6, 12, and 24 h after the recovery.

Time till the first analgesic requirement: which was the time interval from recovery of the patient from anaesthesia till time of his first analgesic request.

Total PCA morphine consumption during the first postoperative 24 h.

PONV: was assessed as number of attacks of nausea or vomiting in the first 24 h after surgery and metoclopramide 10 mg i.v. was given for every attack of nausea or vomiting. The patients were evaluated for any other complications or side effects up to 24 h after the surgery.

Sample size estimation was based on the non-parametric distribution of VAS score with a significance of ($\alpha = 0.05$) and power ($1 - \beta = 0.80$). The primary outcome measure was VAS score at rest 4 h post-operative. The expected reduction in VAS score 4 h post-operative was 0.53 and the expected variability (standard deviation) was 0.7. Mann–Whitney U test as a model was used for calculating the number needed per group based on previous knowledge of an average VAS score of pain after 24 h with Mg + local anaesthesia in epidural space of 1.6 ± 0.7 [16] compared to 2.13 ± 0.64 in group receiving paravertebral local anaesthesia [17]. The minimum number of patients was calculated as 40 per group. To compensate for possible drop-outs we increased the number to 45 for each group.

2.1. Statistical methods

Statistical Package for Social Sciences (SPSS) version 17.0 was used for data analysis. Mean ± standard deviation was used for the description of VAS scores, time to first analgesic requirement and total 24 h morphine consumption. Median and range was used for the description of attacks of vomiting. Parametric and non-parametric independent *t* test compared mean and medians of the 2 study groups. *P* values were set significant at 0.05 level.

3. Results

The present study showed no significant difference between the 2 groups as regards demographic data (Table 1).

Addition of magnesium sulphate to bupivacaine 0.25% in the paravertebral space significantly reduced VAS scores at all time assessment points, both at rest and with shoulder movement (Table 2).

The times to first analgesic request after surgery were 547.8 ± 69.2 and 283.4 ± 77.0 min in group (BM) and group (B), respectively ($P < 0.001$). Furthermore, patients in group (BM) required less amount of morphine in the first 24 h of postoperative period (15.9 ± 3.1 mg) compared to the control bupivacaine group (23.2 ± 3.7 mg) with p-value < 0.001.

The median number of attacks of PONV in patients in group (BM) in the first 24 h after surgery was 0 with range (0–2) which was lower than that of patients in group (B) whose median was 1 and range was (0–3). Less number of patients (12 patients) in the bupivacaine magnesium sulphate group (BM) required metoclopramide as a rescue antiemetic compared to the number of patients in the bupivacaine group (B) which was 25 patients ($P = 0.001$).

Patients of both groups were observed for other complications as respiratory depression, drowsiness and pruritis. None of these complications was reported by the patients of the present study. Complications related to paravertebral block technique, as epidural spread denoted by hypotension, were absent.

4. Discussion

The results of the present study demonstrated that the addition of magnesium sulphate to ultrasound-guided, bupivacaine-induced paravertebral block improves postoperative pain scores and reduces postoperative PCA morphine consumption and opioid-induced side effects in female patients undergoing modified radical mastectomy.

The direct action of magnesium on the peripheral nerves is supported by the study done by Belgin Buyukakilli et al. [18],

Table 1 Demographic data in both groups. Values are means (SD).

	Group (BM) (n = 45)	Group (B) (n = 45)	P-value
Age (years)	55.1 ± 9.8	55.0 ± 10.3	0.96
Weight (kg)	70.7 ± 8.2	71.4 ± 7.2	0.68
Height (cm)	163.5 ± 5.9	164.7 ± 6.0	0.36
Duration of surgery (min)	125.2 ± 19.2	128.6 ± 18.7	0.43

* P value is significant $\leqslant 0.05$.
Group (B) = Control bupivacaine group, Group (BM) = Combined magnesium sulphate and bupivacaine group.

Table 2 Visual analogue scores at rest and with movement. Values are means (SD).

	Group (BM) (n = 45)	Group (B) (n = 45)	P-value
VAS-R 30 min	1.2 ± 0.93	2.6 ± 0.59	<0.001
VAS-M 30 min	3.4 ± 0.95	5.1 ± 1.02	<0.001
VAS-R 2 h	1.5 ± 0.93	2.6 ± 0.54	<0.001
VAS-M 2 h	3.5 ± 1.0	5.5 ± 0.87	<0.001
VAS-R 4 h	1.6 ± 0.81	3.4 ± 0.98	<0.001
VAS-M 4 h	3.1 ± 0.9	5.1 ± 1.20	<0.001
VAS-R 6 h	1.9 ± 0.73	3.4 ± 0.93	<0.001
VAS-M 6 h	3.2 ± 0.82	5.0 ± 1.08	<0.001
VAS-R 12 h	1.3 ± 0.75	2.7 ± 1.13	<0.001
VAS-M 12 h	2.7 ± 1.06	4.2 ± 1.13	<0.001
VAS-R 24 h	1.3 ± 0.62	2.2 ± 0.83	<0.001
VAS-M 24 h	2.8 ± 0.74	4.0 ± 1.08	<0.001

* P value is significant $\leqslant 0.05$.VAS-R: visual analogue scale at rest.VAS-M: visual analogue scale with movement.
Group (B) = Control bupivacaine group, Group (BM) = Combined magnesium sulphate and bupivacaine group.

who found that magnesium added to bupivacaine resulted in better impulse inhibition in a frog sciatic nerve. This was in agreement with what Goyal et al. found in their study [19]. They found that administration of a small dose of magnesium only in the axillary sheath during brachial plexus analgesia resulted in prolonged time of post-operative pain relief with reduction of post-operative analgesic requirement and without any major side effects.

The efficacy of adding magnesium to bupivacaine in paravertebral block to control post-operative pain in thoracic surgery is evaluated in a study done by Ammar and Mahmoud [13]. The results of their study was in agreement with that of our study and this agreement support the good analgesic efficacy of adding magnesium as an adjuvant to bupivacaine in paravertebral block.

Absence of complications related to the paravertebral block technique as pneumothorax and epidural spread may be due to the use of ultrasound guided technique which allows better localization of the needle in the paravertebral space [20]. Expansion of the paravertebral space and displacement of the pleura by the injected medications was an additional sure sign of a good and safe site of the tip of the needle, which minimize the risk of pleural puncture [21].

This study has some limitations: (1) postoperative assessment duration was limited for 24 h. Probably an extended 48–72 h observation period will be more informative, and (2) we have evaluated one relatively small dose level of magnesium sulphate to minimize the possible confounding effects of systemic absorption. However, future studies should consider investigating different dose levels of magnesium sulphate to find out the appropriate safe dose associated with the maximum extension in the duration of paravertebral analgesia.

5. Conclusion

In brief, the results of improved and prolonged analgesia with less opioid related side effects in our study revealed that adding of magnesium sulphate to bupivacaine can improve the clinical profile of ultrasound-guided thoracic paravertebral block in patients undergoing modified radical mastectomy.

Conflict of interest

No conflict of interest.

References

[1] Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society Guidelines and issues in cancer screening. CA Cancer J Clin 2009;59:27–41.
[2] Poleshuck EL, Katz J, Andrus CH, Hogan LA, Jung BF, Kulick DI, Dworkin RH. Risk factors for chronic pain following breast cancer surgery: a prospective study. J Pain 2006;7:626–34.
[3] Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. J Am Med Assoc 2009;302:1985–92.
[4] Pusch F, Freitag H, Weinstabl C, Obwegeser R, Huber E, Wildling E. Single injection paravertebral block compared to general anaesthesia in breast surgery. Acta Anaesthesiol Scand 1999;43:770–4.
[5] Kairaluoma PM, Bachmann MS, Korpinen AK, Rosenberg PH, Pere PJ. Single-injection paravertebral block before general anaesthesia enhances analgesia after breast cancer surgery with

and without associated lymph node biopsy. Anesth Analg 2004;99:1837–43.
[6] Buggy DJ, Kerin MJ. Paravertebral analgesia with levobupivacaine increases postoperative flap tissue oxygen tension after immediate latissimus dorsi breast reconstruction compared with intravenous opioid analgesia. Anesthesiology 2004;100:375–80.
[7] Kairaluoma PM, Bachmann MS, Rosenberg PH, Pere PJ. Pre-incisional paravertebral block reduces the prevalence of chronic pain after breast surgery. Anesth Analg 2006;103:703–8.
[8] Burlacu CL, Frizelle HP, Moriarty DC, Buggy DJ. Fentanyl and clonidine as adjunctive analgesics with levobupivacaine in paravertebral analgesia for breast surgery. Anaesthesia 2006;61(10):932–7.
[9] Bhatnagar S, Mishra S, Madhurima S, Gurjar M, Mondal AS. Clonidine as an analgesic adjuvant to continuous paravertebral bupivacaine for post-thoracotomy pain. Anaesth Intensive Care 2006;34(5):586–91.
[10] Fawcett VY, Haxby EJ, Male DA. Magnesium; physiology and pharmacology. Br J Anaesth 1999;83:302–20.
[11] Wolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain and hypersensitivity states. Pain 1991;44:293–9.
[12] James MFM. Clinical use of magnesium infusions in anesthesia. Anesth Analg 1992;74:129–36.
[13] Ammar AS, Mahmoud KM. Does the addition of magnesium to bupivacaine improve postoperative analgesia of ultrasound-guided thoracic paravertebral block in patients undergoing thoracic surgery? J Anesth 2014;28:58–63.
[14] Hara K, Sakura S, Nomura T, Saito Y. Ultrasound guided thoracic paravertebral block in breast surgery. Anaesthesia 2009;64:223–5.
[15] Howell PR, Gambling DR, Pavy T, McMorland G, Douglas MJ. Patient-controlled analgesia following caesarean section under general anaesthesia: a comparison of fentanyl with morphine. Can J Anaesth 1995;42:41–5.
[16] Farouk S, Ibrahim S. Pre-incisional epidural magnesium provides pre-emptive and preventive analgesia in patients undergoing abdominal hysterectomy. Br J Anaesth 2008;101:694–9.
[17] Das S, Bhattacharya P, Mandal MC, Mukhopadhyay S, Basu SR, Mandolalso BK. Multiple-injection thoracic paravertebral block as an alternative to general anaesthesia for elective breast surgeries: a randomised controlled trial. Indian J Anaesth 2012;56:27–33.
[18] Buyukakilli B, Doruk N, comelekoglu U, Camdeviren H, Gunefi S. Do adjuncts (tramadol and magnesium) potentiate impulse inhibition by a local anesthetic in isolated frog sciatic nerves? Turk J Med Sci 2006;36:201–7.
[19] Goyal P, Jaiswal R, Hooda S, Goyal R, Lal J. Role of magnesium sulphate for brachial plexus analgesia. Internet J Anesthesiol 2008;21(1).
[20] Cowie B, McGlade D, Ivanusic J, Barrington MJ. Ultrasound-guided thoracic paravertebral blockade: a cadaveric study. Anesth Analg 2010;110:1735–9.
[21] Murata H, Salviz EA, Chen S, Vandepitte C, Hadzic A. Ultrasound-guided continuous thoracic paravertebral block for outpatient acute pain management of multilevel unilateral rib fractures. Anesth Analg 2013;116:255–7.