Atracurium mixed with magnesium sulfate versus atracurium alone as adjuvant to lidocaine in intravenous regional anesthesia: A randomized clinical trial

Shaimaa M. Mekkawy, Hamdy A. Youssef, Amr M. Sleem, Ghada M. AboElfadl

Department of Anesthesia and Intensive Care, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Shaimaa M. Mekkawy, Department of Anesthesia and Intensive Care, Faculty of Medicine, Assiut University, Assiut, Egypt.
Tel: +20 100 722 1665; fax: +20 882 333 327; e-mail: toshimaa.abdallah10@yahoo.com

Received 06 August 2019
Accepted 01 October 2019
Published 23 February 2021

Journal of Current Medical Research and Practice
2021, 6:58–64

Back ground
Intravenous regional anesthesia (IVRA) is considered one of the regional techniques used for surgical anesthesia in the upper extremity without the need for general anesthesia. Local anesthetics are used commonly in this method; also, adjuvant drugs are used to increase the quality of the block.

Aims and objectives
This study evaluated the effect of adding either atracurium alone or atracurium plus magnesium added to lidocaine for IVRA on intraoperative and postoperative analgesia, onset and recovery times of sensory and motor blockades, and tourniquet pain.

Patients and methods
Seventy-five patients scheduled for hand or forearm surgery were allocated randomly into three groups. Group A received 3 mg/kg of lidocaine 2%. Group B received 3 mg/kg of lidocaine 2%+2 mg atracurium. Group C received 3 mg/kg of lidocaine 2%+2 mg atracurium mixed with 10 mg/kg magnesium sulfate. All preparations were diluted with saline to a total volume of 40 ml. Postoperative analgesia during the first 24 h, the onset and the recovery times of sensory and motor block, first analgesic request, the tourniquet pain, side effects of the study drugs, and the quality of anesthesia were assessed.

Results
The time to first analgesia requirement was significantly longer in B group than A group and the longest time was recorded in group C. The onset times of sensory and motor blockades were shorter in group B and group C than in group A. Complete sensory and motor blockade occurred in group B and group C earlier than group A. Onset of recovery of sensory and motor blockades postoperatively were longer in group B and group C than in group A.

Conclusion
Adding magnesium sulfate and atracurium combination to lidocaine in IVRA prolonged the time to the first postoperative analgesia requirement and shortened the sensory and motor block onset times.

Keywords:
atracurium, intravenous regional anesthesia, magnesium sulfate

J Curr Med Res Pract 6:58–64
© 2021 Faculty of Medicine, Assiut University
2357-0121

Introduction

Intravenous regional anesthesia (IVRA) was first defined by August Gustav Bier, a German Surgeon, in 1908 for hand and forearm anesthesia [1]. The particular mechanism of its action is not evidently understood. There appear to be numerous and complementary mechanisms for anesthesia and analgesia. Ischemia, acidosis, hypothermia, and asphyxia play a vital role [2].

IVRA is considered one of the regional techniques used for surgical anesthesia in the upper extremity without the need for general anesthesia. Local anesthetics are used commonly in this method; also, adjuvant drugs are used to increase the quality of the block [3].

Lidocaine has a rapid onset of action and moderate duration of action, so itis suitable for local block and surface anesthesia [4]. The effect of lidocaine as a local anesthetic based on its rapid onset of action with a moderate duration. Therefore, lidocaine is suitable for infiltration, block, and surface anesthesia. Longer-acting substances such as bupivacaine are mostly ideal for subdural and epidural anesthesia [5].

Administration of neuromuscular blocking drugs including atracurium (2 mg) and pancuronium (0.5 mg) with a local

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

anesthetic in upper limb IVRA in adults undergoing fracture reduction improves surgical conditions [6,7].

Atracurium is used as an adjuvant in IVRA is because of its influence on muscle spindles; it decreases the central response from those structures, resulting in loss of muscle tone and muscle movements mechanism with a decrease in nervous insults to the brain. In addition, this block of muscle spindles might alleviate muscle spasms and decrease pain both during and after surgery [7]. Combination of atracurium and lidocaine will cause rapid onsed of sensory and motor blockade, a lower pain score, and a lower adverse effect of lidocaine on IVRA alone [5].

Magnesium, which is known to be a 'Natural physiological calcium channel blocker,' is essential in the anti-nociception mechanism. Magnesium has endothelium derived nitric oxide induced vasodilation; thus, it enhances the activity of local anesthetic agents and improves the quality of anesthesia and prolongs motor and sensory blockade [8]. The mechanism of the analgesic action of Mg is still unclear, but a disorder of calcium channels and the N-methyl-D-aspartate (NMDA) receptor appears to play a significant role [9,10]. An additional mechanism is its role in reducing the release of catecholamine with sympathetic stimulation, which decreases peripheral nociception or the surgery stress response [11,12].

The addition of magnesium to lidocaine for IVRA improves the onset time of both sensory and motor blockade, and decreases both tourniquet pain and postoperative pain scores [13].

Aims

This study aims to evaluate and compare the outcome of adding atracurium alone or atracurium plus magnesium as an adjuvant to lidocaine for IVRA for intraoperative and postoperative analgesia, onset and recovery time of sensory and motor blockage, and tourniquet pain.

Patients and methods

This randomized double-blind, controlled clinical trial was conducted in Assiut University Hospital after it was approved by the local research ethics committee of the Faculty of Medicine, Assiut University, Assiut, Egypt. The study was prospectively registered in Clinical Trials.gov (NCT02920905), on 25/8/2016, and carried out from September 2016 to April 2017. A written informed consent was obtained from all patients.

We included patients with American Society of Anesthesiologist grades I and II, between 20 and 40 years of age, with a body weight of 60–90 kg, of both sexes, and scheduled for hand or forearm surgery. Patients with a history of drug allergy, myasthenia gravis, sickle cell anemia, Raynaud's disease, scleroderma, cardiac disease, diabetes mellitus, a history of convulsions, and liver or renal deficiency were excluded from the study.

An online research randomizer (*http://www.randomizer.org*) was used; the study population was allocated randomly to three groups (A, B, C) of 25 patients each. Patients in group A received 3 mg/kg lidocaine 2%. The patients in group B received 3 mg/kg lidocaine 2%+2 mg atracurium. The patients in group C received 3 mg/kg lidocaine 2%+2 mg atracurium mixed with 10 mg/kg magnesium sulfate; all the preparations were diluted to a total volume of 40 ml saline.

Allocations for the three groups studied were set in well-sealed dense envelops, which were opened serially once patients were enrolled in this study. A nurse who was not involved in the study prepared the study drugs according to the study group in identical syringes. The attending anesthesiologist, the doctor, the data collection staff, and the patient were blinded to the allocation of patient groups.

Methods

Two intravenous cannulae were sited: one (22 G) in a vein on the dorsum of the operated hand and the other in the opposite hand. Double tourniquets were sited on the upper arm of the operated hand. The arm was raised up for 2 min to drain blood vessels from blood before inflation of the tourniquet. The upper (proximal) tourniquet was inflated above the systolic blood pressure of the patient by 100 mmHg. Isolation of the arm circulation was confirmed by inspection of the color of the extremity, loss of radial pulse, and loss of pulse oximeter tracking in the ipsilateral index finger. The anesthetic solution was prepared previously by an observer and administered through the 22-G cannula in the operated hand for 90 s.

Evaluation of the onset of sensory blockage by a pin prick was performed at 1 min intervals in the dermatomal sensory distribution of the medial and lateral ante brachial cutaneous, ulnar, median, and radial nerves (0 = sharp, 1 = touch only, and 2 = cannot feel touch). Score 2 was considered to indicate the beginning of complete sensory blockade. The time of onset of sensory blockage was recorded as the time lapsed from drug injection to achievement of sensory block in all dermatomes.

The assessment of the motor block onset was performed by asking the patient to flex and extend his or her

wrist and fingers. The motor block was rated using the modified Bromage score (0 = normal motor function, 1 = reduced motor strength but can move fingers, and 2 = complete motor block). Complete motor block was noted when no voluntary movement was possible.

When the patient complained of discomfort at the proximal tourniquet site, the distal tourniquet was inflated to the same pressure and the proximal one was deflated. Then, the surgeon started the surgery.

The patients were monitored for intraoperative and postoperative complications. In case of occurrence of hypotension (systolic arterial pressure <90 mmHg or a fall of >50 mmHg from the usual value) during the surgery, 5 mg intravenous ephedrine was administered. In case of occurrence of bradycardia (heart rate <50/min), 0.5 mg intravenous atropine was administered. Intravenous 4 mg ondansetron was administered for nausea and vomiting, and oxygen was delivered through a face mask when oxygen saturation decreased to less than 91%.

The tourniquet was not deflated before 30 min and was not kept inflated for more than 2 h.

At the end of surgery, deflation of the tourniquet was performed using a cyclic deflation technique.

Data collection

The onset and recovery times of motor and sensory block were determined. Postoperative analgesia was measured by visual analog scale (VAS) of 0–10 (0 = no pain and 10 = worst pain imaginable) during the first 24 h, and first analgesic request, tourniquet pain, side effects of the study drugs, and quality of anesthesia were evaluated by the patients and the surgeons. The start of sensory block and its duration were measured by response to pin prick at 1 min intervals (0 = sharp, 1 = touch only, and 2 = no touch). Score 2 was considered to indicate the beginning of a complete sensory block. Motor block was measured using a three-point scale for motor function (0 = normal motor function, 1 = reduced motor strength but can move fingers, 2 = complete motor block). Time of onset of upper tourniquet pain was recorded. Tourniquet pain and intraoperative degree of analgesia were evaluated by VAS every 20 min.

Patient and surgeon satisfaction score and quality of anesthesia

At the end of the operation, a resident was asked to grade the surgical conditions using the following numeric scale: excellent = 4, no patient complaint; good = 3, minor complaint without additional analgesics; moderate = 2, complaint that required additional analgesic; and ineffective = 1, patient was administered general anesthesia. At the end of the operation, the surgeon, who was blinded to group assignment, was instructed to evaluate the operative field conditions using the following numeric scale: 0 = unsuccessful; 1 = poor; 2 = acceptable; or 3 = excellent. Patient satisfaction score was verified 24 h postoperatively, whereas surgeon satisfaction score was verified immediately postoperatively. Patient satisfaction score was implicit as 5 = very satisfied, 4 = satisfied, 3 = neutral, 2 = dissatisfied, and 1 = very dissatisfied.

Any complications or side effects (systemic or local) were registered.

Statistical analysis

Our primary end-point was the VAS. The secondary outcomes included sensory and motor block characteristics, patient satisfaction score, surgeon satisfaction score, and adverse effects. On the basis of a previous study [7], to detect a 25% reduction in the VAS score between the three groups studied with alpha error = 0.05, we needed to include 23 patients in each group. This will yield 80% power of the study. Two cases were added to each study to compensate for violation of the study protocol.

Data were presented as median (range), mean ± SD, or percentages according to the type of data. One-way analysis of variance was used to analyze parametric data, the Kruskal–Wallis test was used to analyze nonparametric data, and the χ^2 test was used to analyze between percentages. *P* value less than 0.05 was considered to be nonsignificant.

Results

Patients' and surgical data

Ninety-five patients were evaluated for eligibility. Twelve patients did not fulfill the inclusion criteria, eight patients refused to participate, and the rest of the 75 patients were enrolled randomly in the study, with 25 patients in each group. All these patients completed the study and were analyzed finally. Patients in the three groups were similar in terms of age, sex, weight, type and duration of surgery, and tourniquet time (Table 1).

Onset times of sensory and motor blockades

Onset of sensory block was shorter in group B (4.4 ± 2 min) and in group C (4.4 ± 1.2 min) compared with group A (6.9 ± 2.2 min). Onset of motor block

was shorter in group C (4.6 ± 0.8 min), followed by group B (6 ± 2 min) and group A (11.4 ± 3.3 min); there was a significant difference between the three study groups. Complete sensory and motor block was achieved in group B (9.8 ± 2.5 min; 11.4 ± 2.5 min) and group C (10.2 ± 1.1 min; 11.1 ± 1.81.8 min) earlier than group A (10.9 ± 2.4 min; 17.8 ± 3.8 min). There were statistically significant differences ($P < 0.05$) (Table 2).

Recovery of sensory and motor blockades

Onset of recovery of sensory and motor blockades postoperatively were longer in group B (10 ± 1.9 and 9.2 ± 2.5 min) and group C (9.1 ± 2.1 and 9.8 ± 1.8 min) than in group A (8.2 ± 3 and 3.6 ± 1.7 min). There were statistically significant differences ($P < 0.05$) (Table 2).

Side effects

Oral numbness occurred in two patients in group A and in one patient in group C, and no patients suffered from oral numbness in group B. Dizziness occurred in one patient in group A, with no noted cases of dizziness in the other groups. There were no significant differences among the three groups studied in the prevalence of complications ($P = 0.353$ for oral numbness and $P = 0.363$ for dizziness) (Fig. 1).

Visual analog scale

Intra-operatively, no significant differences were recorded in the intraoperative VAS score between the three groups studied at all measured time points during the operative procedure (Figs. 2 and 3). The postoperative VAS score was significantly lower in group B and group C compared with group A up to 12 h postoperatively; no significant difference was recorded between the groups 24 h after the operation.

Time to first analgesic request

This was significantly longer in group B (37.08 ± 12.1 min) than in group A (24.52 ± 13 min), and the longest time was recorded in group C (90.6 ± 30.6 min). There were statistically significant differences between the three groups (Table 3).

Quality of anesthesia

No significant differences were found among the three study groups in patient and surgeon satisfaction (Table 3).

Table 1 Patient characteristics and basic data

	Group A	Group B	Group C	*P*
Age	30.7±6.8	28.9±5.6	30.3±5.4	0.54
ASA I/II	19/6	17/8	21/4	0.416
Sex (male/female)	19/6	23/2	22/3	0.25
Body weight (kg)	71.8±9.1	69.5±6.4	70.8±4.9	0.519
Height (cm)	162.4±5	160.8±4.4	161.1±5.1	0.480
Type of surgery				
Carpal tunnel	5	2	4	0.895
Plating radius or ulna	4	7	7	
Tendon repair	7	7	7	
Excision head of radius	2	2	4	
Fracture scaphoid	7	7	3	
Duration of surgery (min)	64.9±11.1	62.6±12.5	69.9±9.9	0.073
Tourniquet time (min)	51.2±7.4	53.2±4.2	51.1±4.2	0.302

Data are represented as mean±SD and *n*. ASA, American Society of Anesthesiologists

Table 2 Comparison between the studied groups in terms of sensory and motor block and recovery

	Group A	Group B	Group C	*P*
Onset of sensory block (min)	6.9±2.2	4.4±2	4.4±1.2	0.001
Complete of sensory block (min)	10.9±2.4	9.8±2.5	10.2±1.1	0.176
Onset of motor block (min)	11.4±3.3	6±2	4.6±0.8	0.001
Complete of motor block (min)	17.8±3.8	11.4±2.5	11.1±1.8	0.001
Sensory block recovery time (min)	8.2±3	10±1.9	9.1±2.1	0.043
Motor block recovery time (min)	3.6±1.7	9.2±2.5	9.8±1.8	0.001

Data are represented as mean±SD.

Table 3 Comparison between the studied groups in terms of first time analgesia, and patients' and surgeons' satisfaction

	Group A	Group B	Group C	*P*
First time analgesia	24.5±13.8	37.1±12.1	90.6±30.6	<0.001
Patient satisfaction	3 (2-5)	4 (2-5)	4 (2-5)	0.663
Surgeon satisfaction	3 (3-4)	3 (3-4)	3 (3-4)	0.949

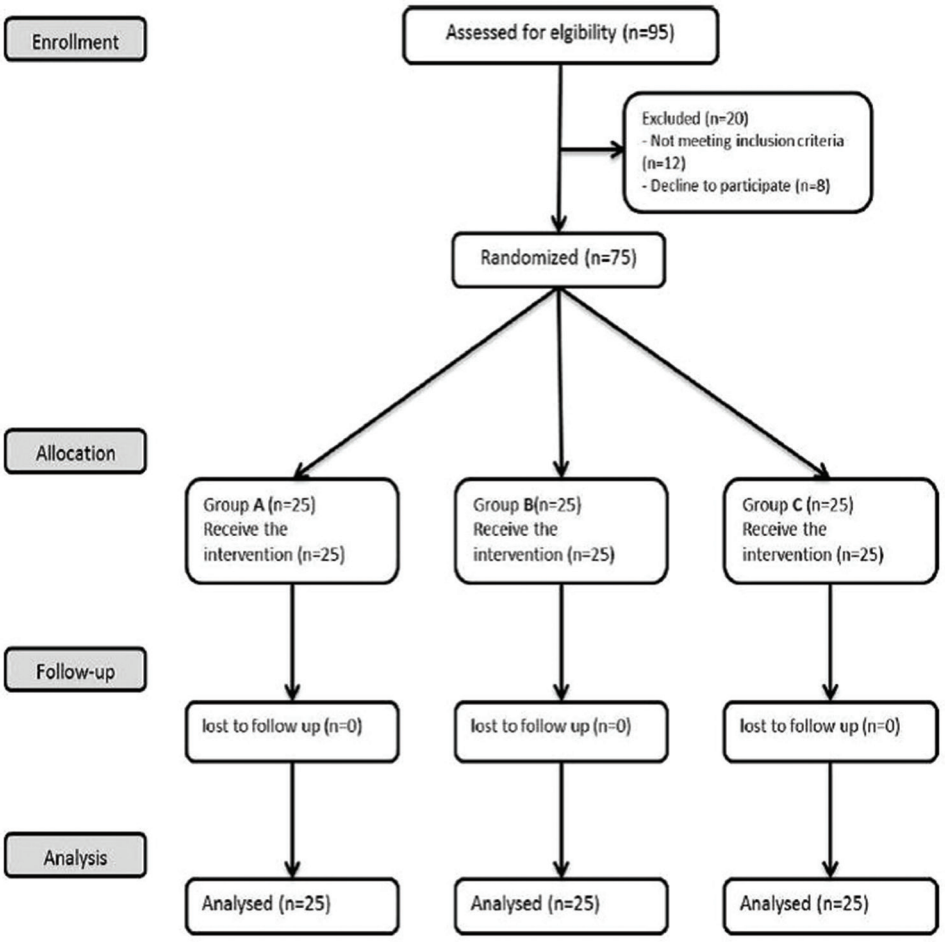
Data are represented as mean±SD, and median (range).

Discussion

One of the major goals in patients undergoing IVRA is pain relief and reducing analgesic needs, thus improving anesthesia quality. IVRA is an easy and effective technique of administering analgesia in a limb by an injection of a local anesthetic intravenously, however, preventing blood to reach the proximal part of the limb by using tourniquet devices. It is performed by increasing pressure to the proximal extremity using the pneumatic tourniquet that isolates the limb from systemic circulation and then injects the local anesthetic agent into the sequestered limb.

The results of this study showed that time to first analgesia request was significantly longer in group B than in group A and the longest time was recorded in group C. The onset time of sensory blockade was shorter in group B and in group C paralleled to group A. Motor

Figure 1



Consort flow chart.

block onset time was shorter in group C, followed by group B and group A; there was a significant difference between the three study groups. Complete sensory and motor block occurred in group B and group C earlier than group A. The onset of recovery of sensory and motor blockades postoperative was longer in group B and group C than in group A. The postoperative VAS score was significantly lower in group B and group C paralleled to group A up to 12 h postoperatively; no significant difference was noted among the groups 24 h after the surgery.

Mirkheshti and his colleagues postulated that adding magnesium to lidocaine (3 mg/kg of lidocaine + 1 g $MgSO_4$) during upper extremity orthopedic surgery with IVRA markedly reduces the period between the administration of the drug and the onset of blockage is significantly reduced. In addition, this drug mixture increased block length of IVRA, whereas the administration of paracetamol did not exert this effect [3].

Choyce and Peng [14] stated that the use of NSAIDs or clonidine as adjuncts to improve postoperative analgesia in IVRA and muscle relaxants improve intraoperative motor block and aid fracture reduction.

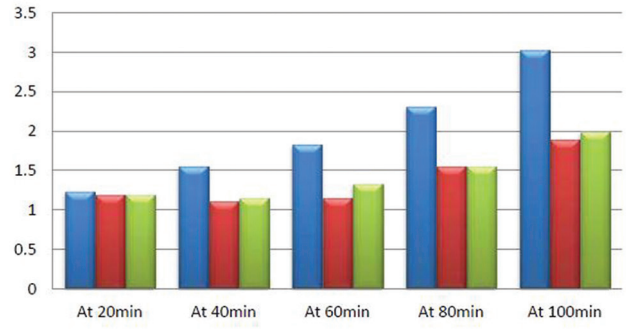
Another study by Hassan Sarhan Haider found that a mixture of ketamine and atracurium added to lidocaine led to quick onset of sensory and motor block, lower VAS scores for pain, and fewer side effects of Bier's block accompany lidocaine alone [15]. In agreement with this, we recorded lower intraoperative VAS and postoperative VAS in group B than in group A.

Elhakim and Sadek [7] concluded that adding atracurium to lidocaine improves the operative situation during IVRA, with less pain during and after surgery.

Flamer and Peng [16] stated in their review that the combination of fentanyl and muscle relaxants (pancuronium, atracurium, mivacurium, cisatacurium) can yield the same value of IVRA with a 50% decrease in the local anesthetic dose, but with a potentially slower onset of sensory block.

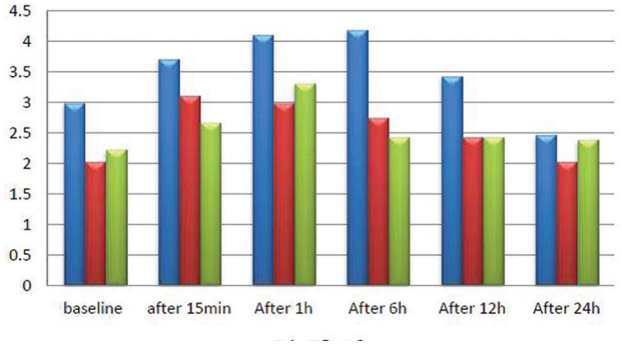
Wahba and Tammam studied three groups of 20 patients each: the R group, which received IVRA with

Figure 2



Intraoperative median range of VAS. VAS, visual analog scale.

Figure 3



Postoperative VAS. VAS, visual analog scale.

ropivacaine 0.2%; the RM group, which received IVRA using ropivacaine 0.2% and $MgSO_4$ 10 mg/kg; and the RMV group, which received IVR using ropivacaine 0.2% and a single systemic intravenous dose of $MgSO_4$ 30 mg/kg. They found that the addition of magnesium to ropivacaine in the IVRA increased the block quality and decreased tourniquet discomfort, and systemic administration of magnesium led to decreased morphine consumption and postoperative pain [17].

Bansal *et al.*[18] concluded that adding both magnesium sulfate and nitroglycerin to lidocaine in IVRA led to early onset of sensory blockage and sustained postoperative analgesia, with no side effects.

Tramer and Glynn[19] used 500 mg $MgSO_4$ to treat chronic limb pain with IVRA and showed that adding magnesium to lidocaine increased the block quality and prolonged the analgesia. According to another study, the response times for sensory and motor blockages in magnesium sulfate were statistically shorter.

Further studies with different doses of magnesium and atracurium will help determine the adequate dose for the best clinical and postoperative analgesia. Other studies with different combinations should be tried.

The limitations in this study were as follows: first, the sample size was small. Second, we did not measure the magnesium level in the plasma.

Further studies should be carried out on larger sample sizes, measuring the magnesium levels in the plasma, and using different kinds of combinations.

Conclusion

The addition of the combination of magnesium sulfate and atracurium to lidocaine shortened the sensory and the motor blockade onset times, with better quality of anesthesia, and prolonged the time of the first postoperative analgesic requirement. The addition of magnesium and atracurium to a local anesthetic lidocaine in IVRA was effective.

Acknowledgements

Shaimaa M. Mekkawy and Amr M. Sleem: data collection and preparation. Hamdy A. Youssef: Study design, data analysis, manuscript writing and preparation. Ghada Mohammad AboElfadl: study design, manuscript writing, and editing.

The authors are grateful to the colleagues and staff of the operating theater and PACU for their co-operation in data collection. The authors thank the Department of Orthopedic and Trauma Unit.

Support was provided solely from departmental resources.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Bier A. A new method for local anaesthesia in the extremities. Ann Surg 1908; 47:2.

2 Rosenberg PH, Heavner JE. Multiple and complementary mechanisms produce analgesia during intravenous regional anesthesia. Anesthesiology 1985; 62:840–842.

3 Mirkheshti A, Aryani MR, Shojaei P, Dabbagh A. The effect of adding magnesium sulfate to lidocaine compared with paracetamol in prevention of acute pain in hand surgery patients under intravenous regional anesthesia (IVRA). Int J Prev Med 2012; 3:616–621.

4 Fernando R, Gerard W. Ostheimer 'what's new in obstetric anesthesia' lecture. Anesthesiology 2007; 106:615–621.

5 Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. Cochrane Database Syst Rev 2014; 24:Cd010958.

6 McGlone R, Heyes F, Harris P. The use of muscle relaxant to supplement local anaesthetics for Bier's blocks. Arch Emerg Med 1988; 5:79–85.

7 Elhakim M, Sadek RA. Addition of atracurium to lidocaine for intravenous

regional anaesthesia. Acta Anaesthesiol Scand 1994; 38:542–544.

8 Turan A, Memis D, Karamanlioglu B, Guler T, Pamukcu Z. Intravenous regional anesthesia using lidocaine and magnesium. Anesth Analg 2005; 100:1189–1192.

9 Weir C. *Stoelting's anesthesia and co-existing disease*. Oxford: Oxford University Press; 2013.

10 Ozcan PE, Tugrul S, Senturk NM, Uludag E, Cakar N, Telci L, *et al*. Role of magnesium sulfate in postoperative pain management for patients undergoing thoracotomy. J Cardiothorac Vasc Anesth 2007; 21:827–831.

11 Koinig H, Wallner T, Marhofer P, Andel H, Horauf K, Mayer N. Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg 1998; 87:206–210.

12 Haryalchi K, Ghanaie MM, Yaghoubi Y, Milani F, Faraji R. An assessment of changes in the magnesium level during gynecological abdominal surgeries. J Basic Clin Reprod Sci 2013; 2:110–114.

13 Estebe JP, Gentili ME, Langlois G, Mouilleron P, Bernard F, Ecoffey C. Lidocaine priming reduces tourniquet pain during intravenous regional anesthesia: a preliminary study. Reg Anesth Pain Med 2003; 28:120–123.

14 Choyce A, Peng P. A systematic review of adjuncts for intravenous regional anesthesia for surgical procedures. Can J Anaesth 2002; 49:32–45.

15 Haider H, Mahdi FA. The combination effect of lidocaine, ketamine and atracurium in intravenous regional anesthesia. Al Kindy Collegue Med J 2013; 9:61–63.

16 Flamer D, Peng PW. Intravenous regional anesthesia: a review of common local anesthetic options and the use of opioids and muscle relaxants as adjuncts. Local Reg Anesth 2011; 4:57–76.

17 Wahba SS, Tammam TF. Intravenous regional anesthesia: effect of magnesium using two different routes of administration. Ain-Shams J Anaesthesiol 2014; 7:65–69.

18 Bansal P, Baduni N, Bhalla J, Mahawar B. A comparative evaluation of magnesium sulphate and nitroglycerine as potential adjuncts to lidocaine in intravenous regional anaesthesia. Int J Crit Illn Inj Sci 2015; 5:27–31.

19 Tramer MR, Glynn CJ. Magnesium Bier's block for treatment of chronic limb pain: a randomised, double-blind, cross-over study. Pain 2002; 99:235–241.