Archives of Anesthesiology and Critical Care (Winter 2023); 9(1): 40-45.

Available online at http://aacc.tums.ac.ir

Research Article

Evaluating the Effects of Lidocaine Alone versus Combination of Lidocaine with Pethidine for the Intravenous Regional Anesthesia in Upper Limb Soft Tissue Surgery

Afshin Amini, Arash Farbood, Saman Asadi, Heidar Safari, Mahsa Ranjbar*

Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

ARTICLE INFO

Article history:
Received 09 April 2022
Revised 30 April 2022
Accepted 14 May 2022

Keywords:
Anesthesia;
Lidocaine;
Meperidine;
Morphine;
Analgesia

ABSTRACT

Background: Intravenous regional anesthesia (IVRA) has been used as a common anesthetic technique for several types of operations. However, there are various concerns regarding the efficacy of this anesthetic method. The aim of this study was to evaluate the effects of lidocaine alone versus concomitant use of lidocaine and pethidine for the IVRA in upper limb surgery.

Methods: In this randomized, double-blind, controlled clinical, 50 eligible individuals were randomly divided to receive either a combination of 1.5 mg/kg lidocaine 2% and 1.5 mg/kg pethidine or placebo (3 mg/kg lidocaine 2%) for IVRA. After the surgery, the onsets and durations of sensory and motor block, the pain intensity in recovery room, the subjects' first demand of morphine, and the total amount of morphine injected within 24 hours were measured.

Results: The combination of lidocaine and pethidine was significantly effective in accelerating the onset of both sensory and motor blocks [(P=0.001), (P=0.001), respectively]. However, no differences were found between groups in sensory and motor block durations after surgery. Intervention with lidocaine plus pethidine caused a significant reduction of the pain intensity in recovery room (P=0.02). Also, concomitant use of lidocaine and pethidine led to a longer time of the first demand of morphine (P=0.04). Moreover, the total amount of morphine injected within 24 hours after surgery was considerably lower in individuals treated by lidocaine plus pethidine (P=0.003).

Conclusion: The results of the current study suggest that adding pethidine to lidocaine can be considered as an appropriate approach for better management of IVRA.

Intravenous regional anesthesia (IVRA; Bier block) is known as one of the most reliable and efficient anesthetic procedures which is desirable for short-term surgical operations on the extremities [1-2]. Additionally, IVRA can be considered as a cost-effective method in comparison with general anesthesia and brachial plexus blocks for upper limb soft tissue surgeries with an ambulatory basis [3]. However, the efficacy of IVRA technique has been limited due to its several defects including concern of local anesthetic toxicity, delayed onset, impaired muscle relaxation, tourniquet pain, insufficient postoperative pain relief, and cardiorespiratory depression [4-6]. The toxicity might be triggered by leaking past the tourniquet following the injection procedure, which can be related to the failure of the tourniquet or a rise in venous pressure distal to the tourniquet [7].

Hence, it would be preferable to combine additives with local anesthetics in order to alleviate the IVRA disadvantages [8]. Based on earlier studies, the adjuncts used were opioids (fentanyl, meperidine, morphine, sufentanil), tramadol, nonsteroidal anti-inflammatory

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: af.amini1400@gmail.com

drugs (NSAIDs; ketorolac, tenoxicam, acetyl-salicylate), clonidine, muscle relaxants (atracurium, pancuronium, mivacurium), alkalinization with sodium bicarbonate, potassium and temperature [4].

Opioids are one of the well-known class of medications with a wide range of clinical effects which are structurally similar to the natural plant alkaloids derived from the Papaveraceae family [9]. Pethidine (also known as meperidine) is a synthetic opioid analgesic which has been highlighted regarding its unique medical benefits [10]. Based on the previous studies, it has been shown that using pethidine as the single anesthetic might be helpful through the quality of sensory and motor block in certain tissue surgeries [11]. Also, pain-relieving and long-lasting analgesic properties of systemically administered pethidine have been documented in the past experiments [12-13]. Moreover, the use of pethidine as part of IVRA method may result in a reduction in the dose of lidocaine required for an effectual intraoperative analgesia and also protect against the risk of systemic toxicity of local anesthetics in cuff leakage condition [14].

Therefore, in the present study, it was hypothesized that adding pethidine as an adjunct to lidocaine in IVRA might be associated with appropriate management of upper limb soft tissue surgery.

Methods

Fifty eligible individuals (18-60 years old) who were candidate for the upper limb surgery with the American Society of Anesthesiology (ASA) score ≤ 2, were recruited from Shahid Chamran Hospital, Shiraz, Iran. The sample size was measured according to the previous study with regard to the type I error of 5% ($\alpha = 0.05$), and type II error of 20% [15]. The exclusion criteria were as follows: having history of chronic diseases including heart disease, high or low blood pressure, bradycardia, hyperthyroidism, cardiac blocks, peripheral neuropathy, suffering from coagulation disorders, topical infections, and deformities with musculoskeletal of the upper limb, taking adrenoceptor agonists or antagonists, smoking or any drug addiction, pregnancy and lactation, having history of severe side effects or allergic symptoms with the current study medications, and lack of adherence to the study protocol.

All participants were informed about the study objectives and signed the written consent form. The procedure of this study was conducted according to the Declaration of Helsinki. It was also approved by the Ethics Committee on Human Experimentation of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.574). Moreover, this trial was registered at the Iranian Registry of Clinical Trials (ID number: IRCT20141009019470N115, link: https://www.irct.ir/search/result?query=IRCT20141009019470N115).

Study Design

This randomized, double-blind, controlled clinical trial was conducted in Shiraz, Iran. All participants were randomly assigned in two equal groups of intervention and control (25 persons in each group) as follows:

Intervention group: received lidocaine 2% (Caspian Tamin, Pharmaceutical Co. Rasht, Iran) in a dose of 1.5 mg/kg body weight + pethidine (Daroupakhsh, Pharmaceutical Co. Tehran, Iran) in a dose of 1.5 mg/kg body weight at the onset of the surgery to induce bier block

Control group: received lidocaine 2% in a dose of 3 mg/kg body weight at the onset of the surgery to induce bier block

The randomization was conducted using computer-generated randomization, and a trained clinician performed the randomized allocation sequence and assigned subjects to the intervention and control groups. In both study groups, the same 40 cc syringes and the same drug color were used. After implanting a cannula in the distal limb, the patient was asked to hold the injured hand up for 10 minutes. Then, we placed a dual-port tourniquet (containing proximal cuff and distal cuff) on the proximal of the limb. At first, we filled the proximal cuff for all subjects up to 300 mmHg so that the patient's radial pulse could not be felt. Afterwards, the patient's medicine, which was given to the doctor unspecified, was injected slowly for 90 seconds. When the patient complained of severe pain or tingling at the site of the tourniquet, we first inflated the distal cuff and then released the proximal cuff. Meanwhile, intravenous injection of 1 mg midazolam (Chemidarou, Pharmaceutical Co. Tehran, Iran) and 1 µg/kg fentanyl (Caspian Tamin, Pharmaceutical Co. Rasht, Iran) were used for the sedation of all study participants.

Assessment of the study variables

All data were collected by trained researchers and explicit instructions were given to all participants.

Demographic measurements were performed at entry of the intervention. Body weight was measured using a digital scale (Seca, Hamburg, Germany) with an accuracy of 0.1 kg with light clothes and no shoes.

The assessment of the onset of sensory nerve block was carried out using pin prick test in the areas of four main branches of hand nerves and with a 25-gauge needle every 30 seconds. The onset of motor nerve block was also evaluated, considering the capabilities of flexion and extension of wrist and fingers every 30 seconds. Moreover, the time durations of both sensory block and motor block were calculated. The shortest safe time to open the tourniquet cuff was 25 minutes after injection, but patients were closely monitored for the risk of local anesthetic toxicity. Furthermore, the pain intensity was assessed in the recovery room every 15 minutes using numerical rating scale (NRS). A patient-controlled analgesia (PCA) pump with morphine (Daroupakhsh, Pharmaceutical Co. Tehran, Iran) was used in order to control patients' pain after the surgery. Meanwhile, we

measured the time of the first demand for the morphine injection and the total amount of morphine injected within 24 hours after surgery in all participants.

Statistical analysis

The Statistical Package for Social Sciences (version 22.0; SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. At first, the Kolmogorov–Smirnov test was used to assess the normal distribution of the data. Independent samples t-test was performed in order to evaluate differences between the intervention and control group. Qualitative variables were compared using the chi square test. Also, repeated measures ANOVA was used to compare the mean pain intensity between groups at different measurement times. All the differences were considered statistically significant at P≤0.05.

Results

The general characteristics of the two study groups have been reported in (Table 1).

As the table depicts, there were no statistically significant differences among the study groups at the baseline period. In the course of intervention, two subjects were excluded from the study (Figure 1). No serious side effects were detected in the two study groups.

Sensory and motor blocks

The mean values of sensory block onset, motor block onset, duration of the sensory block, and duration of the motor block in each study group have been presented in (Table 2). The sensory block onset showed statistically significant decrease in the intervention group compared to the control group (P=0.001). Also, in comparison with the control group, there was a significant reduction of motor block onset in patients treated with pethidine (P=0.001). However, at the end of the study, no significant difference was found in terms of the sensory and motor block durations in both study groups [(P=0.52), (P=0.98), respectively].

The pain intensity

Participants were monitored every 15 minutes for the pain intensity from the beginning to the end of the being in the recovery room. The time-group interaction showed that during the recovery room period, the pain intensity was notably lower in the intervention group when compared to the control group (P=0.02) (Table 3).

Morphine injection

Compared to the individuals in control group, the time of the first demand for the morphine injection was significantly longer in the intervention group (P=0.04) (Table 4). Additionally, the total amount of morphine injected within 24 hours after surgery was significantly lower in subjects treated by pethidine compared to the control group (P=0.003) (Table 5).

Table 1- The subjects' general characteristics

Parameters	Total (n=50)	Control group (n=25)	Intervention group (n=25)	P value
Age (Year)a	38.51±13.90	36.34±13.24	41.26±14.54	0.25*
Gender (male)b	32 (64%)	19 (76%)	13 (52%)	0.07**
Weight (Kg)a	68.92±14.95	69.47±9.5	68.17±20.48	0.78*

a: Data expressed as Mean±SD, b: Data expressed as n (%), * Obtained from the Independent-Sample T Test,

** Obtained from the Chi-squared test, P-value≤0.05 was considered as significant

Table 2- The comparison between sensory block onset, motor block onset, duration of the sensory block, and duration of the motor block in both study groups

Parameters (min)	Control group (n=25)	Intervention group (n=25)	P value*
Sensory block onset	4.33±0.91	2.37±1.13	0.001
Motor block onset	11.66±3.50	6.75±1.89	0.001
Sensory block duration	64.16±31.02	59.29±21.33	0.52
Motor block duration	61.45±35.10	61.25±31.05	0.98

Data expressed as Mean±SD, * Obtained from the Independent-Sample T Test, P-value≤0.05 was considered as significant

Table 3- The comparison between patients' pain intensity in the recovery room in both study groups every 15 min

Groups	min: 15	min: 30	min: 45	min: 60	P value*		
					Time	Group	Time∗ Group
Control group (n=25)	3.66 ± 2.25	3.54 ± 1.93	3.2 ± 1.53	2.58 ± 1.41	0.131	0.001	0.02
Intervention group (n=25)	0.78 ± 1.31	1.0 ± 1.25	1.12 ± 1.3	1.0±1.12			

Data expressed as Mean±SD, * Obtained from the Repeated Measures analysis, P-value≤0.05 was considered as significant

Table 4- The comparison of the time for the subjects' first demand of morphine after opening the tourniquet between the two study groups

Parameter	Control group (n=25)	Intervention group (n=25)	P value*
first demand for morphine injection (min)	32.05±7.62	73.36±10.78	0.04

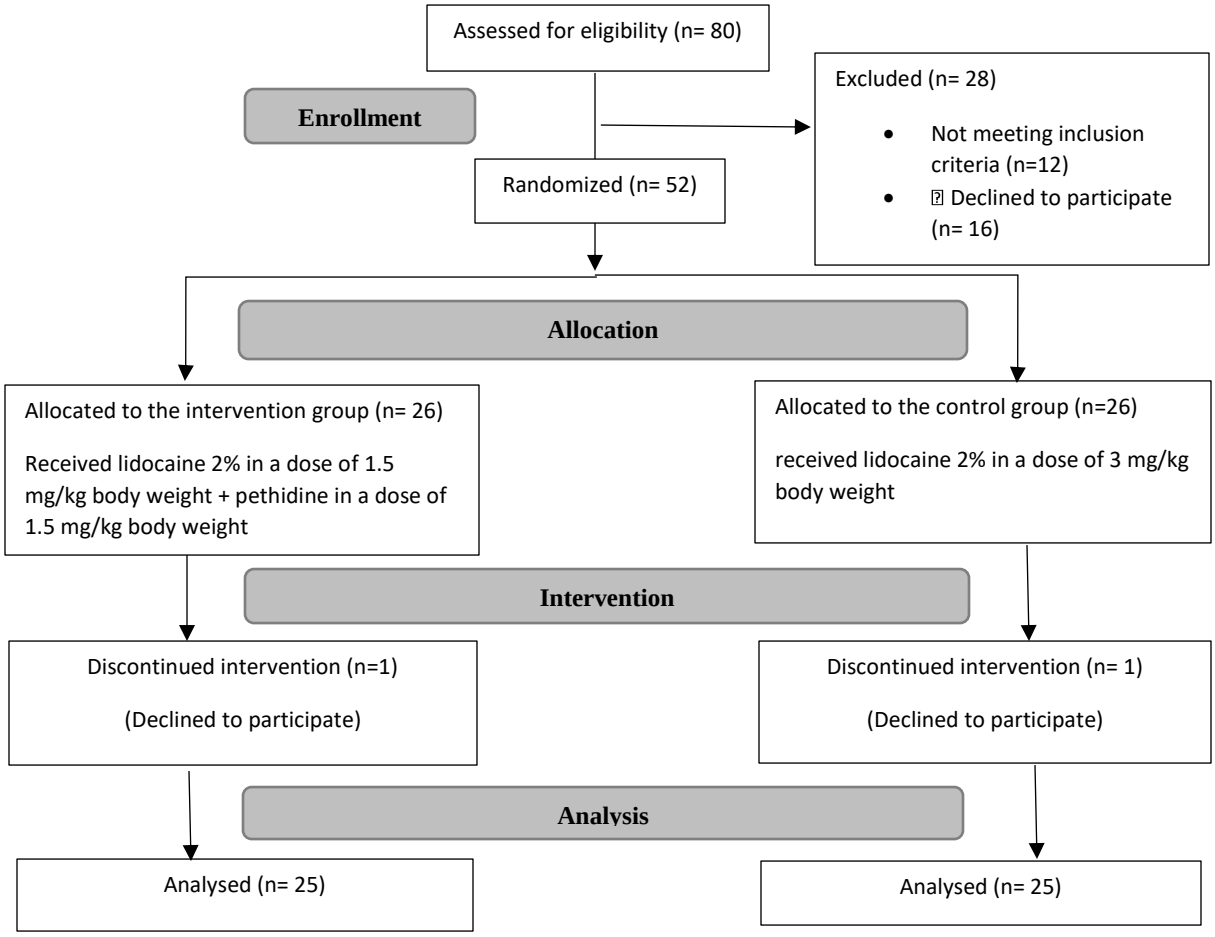
Data expressed as Mean±SD, * Obtained from the Independent-Sample T Test, P-value≤0.05 was considered as significant

Table 5- The comparison of total amount of morphine injected within 24 hours after surgery between the two study groups

Parameter	Control group (n=25)	Intervention group (n=25)	P value*
Total amount of morphine injection (mg/day)	5.54±2.14	2.12±2.21	0.003

Data expressed as Mean±SD, * Obtained from the Independent-Sample T Test, P-value≤0.05 was considered as significant

Figure 1- Consort flow diagram of trial



Discussion

According to the results of the current study, adding pethidine as a synthetic opioid analgesic to lidocaine resulted in considerable improvements in terms of patients' pain intensity in the recovery room, time of the both sensory and motor block onsets, total amount of morphine injection, and the time of the subjects' first demand for morphine after opening the tourniquet.

Nowadays, the pace of surgical operations requires rapid and efficient local anesthesia methods. Although the IVRA is one such technique, but it has been limited by concerns regarding the delayed onset, tourniquet pain, inadequate postoperative pain relief [4, 16].

Previous studies have shown that combine opioids (fentanyl, pethidine) or a muscle relaxant (atracurium, pancuronium) with local anesthetics may play an important role for improving the quality of anesthesia and postoperative analgesia [4, 17]. In accordance with our study results, in 2015, Saryazdi et al. [18] investigated the comparative evaluation of adding different opioid (pethidine, morphine, buprenorphine, or fentanyl) to lidocaine in duration and quality of axillary brachial plexus block. They suggested that adding morphine or pethidine to lidocaine could be superior to other study opioids due to better quality and quantity of motor blockade and the faster block initiation. In addition, Hasannasab et al. [19] found that using pethidine as an adjunct to lidocaine for upper limb IVRA could result in delayed postoperative pain compared to lidocaine alone. The peripheral underlying mechanism of the analgesic effect of pethidine may be mediated by either the local anesthetic properties of pethidine or to the action of pethidine on peripheral opioid receptors [5]. Moreover, pethidine has been shown to reduce vascular resistance in the hands and forearms, which is believed to be a local action of this opioid. Thus, this vasodilation effect may cause solutions containing pethidine to spread faster to the hands and forearms and decrease the time of both sensory and motor block onsets [11, 20]. In one study, Armstrong et al. [11] examined the effects of adding pethidine to prilocaine 0.25% for IVRA in healthy volunteers. In agreement with our findings, the researchers reported that the time of sensory and motor block onset and also the tourniquet pain at ten minutes' inflation were significantly lower in patients treated with pethidine. Furthermore, Enayati et al. [21] showed longer duration of analgesia with pethidine usage, comparing to lidocaine alone in spinal anesthesia for cesarean section. In a study by Abdulla and Fadhil (5) they showed that adding fentanyl (50 µg) and pancuronium (0.5 mg) to 100 mg lidocaine improved the quality of analgesia compared to lidocaine alone after the surgery. Similarly, Nishikawa's research found that adding fentanyl to anesthetics may extend the duration of analgesia for individuals after surgical operation [22]. There are also convincing reports regarding the postoperative pain relieving effects of opioids. Consistent with the current findings, it has been documented that pethidine may reduce the first demand for analgesic agents (acetaminophen/codeine) in the first 24 hr after surgery [14]. Likewise, in one study by Shad Aldine et al. The tramadol as an additive to IVRA effectively reduced both the postoperative pain intensity and the need for postoperative analgesia [23].

Our findings should be interpreted while considering the main limitations. The mean values of time duration of upper limb soft tissue surgery had to be measured for better comparison of the two study groups. As a result of limited funding, important biochemical parameters related to the postoperative inflammatory response at the site of surgical trauma such as histamine, serotonin, bradykinins and metabolites of cyclooxygenase and lipoxygenase pathways were not measured. Hence, future well-designed studies are needed to evaluate other specific markers which may clarify the beneficial underlying mechanisms related to the effects of adding pethidine to lidocaine for IVRA in upper limb soft tissue surgery.

Conclusion

The results of the present study suggest that adding pethidine to lidocaine can be considered as an appropriate approach for the better management of IVRA in upper limb soft tissue surgery.

References

[1] Turan A, Memis D, Karamanlioglu B, Güler T, Pamukçu Z. Intravenous regional anesthesia using lidocaine and magnesium. Anesth Analg. 2005;100(4):1189-92.

[2] 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(9):616-21.

[3] Chan VW, Peng PW, Kaszas Z, Middleton WJ, Muni R, Anastakis DG, et al. A comparative study of general anesthesia, intravenous regional anesthesia, and axillary block for outpatient hand surgery: clinical outcome and cost analysis. Anesth Analg. 2001; 93(5):1181-4.

[4] Choyce A, Peng P. A systematic review of adjuncts for intravenous regional anesthesia for surgical procedures. Can J Anaesth. 2002; 49(1):32-45.

[5] Desai SN, Santhosh M. A randomized, double blind comparison of pethidine and ketoprofen as adjuvants for lignocaine in intravenous regional anaesthesia. Braz J Anesthesiol. 2014;64(4):221-6.

[6] Verma R, Hasnain S, Sreevastava D, Murthy T. Anaesthetic management of forearm fractures using a combination of haematoma block and intravenous regional anaesthesia. Med J Armed Forces India. 2016; 72(3):247-52.

[7] Singh R, Bhagwat A, Bhadoria P, Kohli A. Forearm IVRA, using 0.5% lidocaine in a dose of 1.5 mg/kg with ketorolac 0.15 mg/kg for hand and wrist surgeries. Minerva Anestesiol. 2009; 76(2):109-14.

[8] Sen H, Kulahci Y, Bicerer E, Ozkan S, Dagl G, Turan A. The analgesic effect of paracetamol when

added to lidocaine for intravenous regional anesthesia. Anesth Analg. 2009; 109(4):1327-30.
[9] Kerrigan S, Goldberger BA. Opioids. Principles of forensic toxicology: Springer; 2020. p. 347-69.
[10] Clark RF, Wei EM, Anderson PO. Meperidine: therapeutic use and toxicity. J Emerg Med. 1995;13(6):797-802.
[11] Armstrong P, Morton C, Nimmo A. Pethidine has a local anaesthetic action on peripheral nerves in vivo: addition to prilocaine 0.25% for intravenous regional anaesthesia in volunteers. Anaesthesia. 1993; 48(5):382-6.
[12] Tsui MH, Ngan Kee WD, Ng FF, Lau TK. A double blinded randomised placebo-controlled study of intramuscular pethidine for pain relief in the first stage of labour. BJOG. 2004; 111(7):648-55.
[13] Unlugenc H, Vardar MA, Tetiker S. A comparative study of the analgesic effect of patient-controlled morphine, pethidine, and tramadol for postoperative pain management after abdominal hysterectomy. Anesth Analg. 2008; 106(1):309-12.
[14] Reuben SS, Steinberg RB, Lurie SD, Gibson CS. A dose-response study of intravenous regional anesthesia with meperidine. Anesth Analg. 1999; 88(4):831-5.
[15] Priyamani M, Sreekala K. Comparative Evaluation of Lignocaine 0.5% and Lignocaine 0.5% with Pethidine for Intravenous Regional Anaesthesia in Upper Limb Surgery. J Med Scie and Clinical Res. 2017;5(11):30309-15.
[16] Johnson CN. Intravenous regional anesthesia: new approaches to an old technique. CRNA. 2000; 11(2):57-61.
[17] Reuben SS, Steinberg RB, Lurie SD, Gibson CS. A dose-response study of intravenous regional anesthesia with meperidine. Anesth Analg. 1999; 88(4):831-5.
[18] Saryazdi H, Yazdani A, Sajedi P, Aghadavoudi O. Comparative evaluation of adding different opiates (morphine, meperidine, buprenorphine, or fentanyl) to lidocaine in duration and quality of axillary brachial plexus block. Adv Biomed Res. 2015; 4:232.
[19] Hasannasab B, Soleymani A, Matloub M, Amri P. Comparison of the effects of pethidine plus lidocaine and lidocaine alone on depth and duration of post operative analgesia in IV block of upper limb. Journal of Babol University of Medical Sciences. 2004; 6(2):25-9.
[20] Pauca A. Effect of pethidine premedication and halothane anaesthesia on upper limb blood flow. Br J Anaesth. 1992; 68(6):621-2.
[21] Enayati H, Moudi Z, Tirgar Fk, Dashipour A, Shahsavani A. A Comparison of Effects of Lidocaine 5%, Lidocaine 5% Plus Pethidine 5% And Pethidine 5% In Spinal Anesthesia for Cesarean Section. Zahedan Journal of Research in Medical Sciences. 2007; 9(2):77-85.
[22] Nishikawa K, Kanaya N, Nakayama M, Igarashi M, Tsunoda K, Namiki A. Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. Anesth Analg. 2000; 91(2):384-7.
[23] Sahmeddini MA, Khosravi MB, Seyedi M, Hematfar Z, Abbasi S, Farbood A. Comparison of magnesium sulfate and tramadol as an adjuvant to intravenous regional anesthesia for upper extremity surgeries. Anesth Pain Med. 2017; 7(6):e57102.