RESEARCH ARTICLE

The Effect of Lidocaine Infusion on the Acute Pain after the Surgery of Tibia Fracture under General Anesthesia

Reza Akhondzadeh^{1,2*}, Mohammad Reza
Pipelzadeh², Saeed Rezaee³, Vahid Salehi¹

¹Department of Anesthesiology, Pain Research Center, Ahvaz
Jundishapur University of Medical Sciences, Ahvaz, Iran.

²Pain Research Center, Ahvaz Jundishapur University of Medical
Sciences, Ahvaz, Iran.

³Pharmaceutics Department, Ahvaz Jundishapur University of
Medical Sciences, Ahvaz, Iran.

Study Area: Ahvaz, Iran

Coordinates: 31°19'13"N; 48°40'09"E

Key words: Post-operative pain, Tibia fracture

All of the protocols and experimental procedures of this study were approved by the local ethics committee of AJUMS, Ahvaz, Iran, registered in the Iranian Registry of Clinical Trial (Code: IRCT201104306337N1).

Abstract

Acute postoperative pain is one of the most important causes of the patients' anxiety, which can lead to chronic pain through stimulating the endocrine responses. Preemptive analgesic approach during perioperative period can reduce postoperative pain complications and the therapeutic costs. Lidocaine is an amide local anesthetic agent with analgesic effects even in a low dose of systemic administration and few side effects. In the present study, a randomized clinical trial conducted on 48 patients (age 18 to 50 yrs.) admitted for surgery of tibial fracture types I or II, the effects of lidocaine infusion on the postoperative pain was tried to understand. The pain intensity of the patients was evaluated by a Visual Analog Scale at 1, 2, 4, 12, 16, 20, and 24 hr post-surgery. The results show that the intravenous infusion of lidocaine during surgery reduced the tibial fracture postoperative pain that significantly reduced the dose of systemic administration of opioid for the patients. Conclusively, the intravenous infusion of lidocaine during surgery can be a good option for the patients undergoing tibial fracture class I and II surgeries.

Introduction:

Postoperative acute pain is associated with a wide range of adverse effects and complications, its efficient management and control must be the therapeutic priority in all types of surgeries (Fishman *et al.*, 2010). The transduction of the painful stimulus from the peripheral nerves to the spinal cord and supraspinal centers triggers the neuroendocrine response. The main neuroendocrine response to such pain stimulus is activation of the Hypothalamic- Pituitary- Adrenal (HPA) axis that increases the sympathetic tone, the catecholamines, and the secretion of the catabolic hormones (Akhondzadeh *et al.*, 2017). Uncontrolled pain after surgery causes several acute complications such as coagulation disorders, hemorrhage, thrombosis, immune suppression, hyperglycemia, slow wound healing, intensification of the sympathetic system, blood pressure increase, risk of Myocardial Infarction (MI), dysfunction in bowel movements, and reduced activity and dysfunction of the respiratory system (Nesioonpour *et al.*, 2014). Preemptive analgesic approach during perioperative period can reduce postoperative pain complications, hospitalization

period and consequently the therapeutic costs. In a preemptive analgesic strategy, different methods are used before and during operation to prevent the stabilization of the afferent nerves, which reinforce the postoperative pain toward the central nervous system (Akhondzadeh *et al.*, 2017). Epidural analgesia, systemic opioids, local anesthetics, and non-steroidal anti-inflammatory drugs (NSAIDs) are common methods used in preemptive analgesic approaches (Ballantyne, 2006; Nesioonpour *et al.*, 2014). Each of these methods and drug administration has their own advantages and disadvantages. For example, using the local infiltration techniques, which are usually among the invasive and time- consuming, mostly cause short-term analgesia and need adequate experience of the therapeutic staff (Fishman *et al.*, 2010). The use of neuraxial and epidural techniques can impose different side effects such as epidural hematoma, catheter displacement; and unwanted hemodynamic and motor sensory changes (Block *et al.*, 2003; Brown *et al.*, 2004; Kehlet & Wilmore, 2002). NSAIDs cause restrictions on their usage because of creating the disorders of hemostasis and kidney function and causing gastrointestinal (GI) bleeding (Kasper *et al.*, 2015). Systemic opioids have

*Corresponding Author: akhondzadeh-r@ajums.ac.ir

RESEARCH ARTICLE

restrictions for their usage due to the risk of nausea and vomiting, sedation, respiratory depression, tolerance, and dependence (Brunton *et al.*, 2011).

Tibial fracture operations are among of the most prevalent operations in orthopedics that are conducted under general anesthesia or neuraxial anesthesia. Effective control of the relevant pain after the operation of the tibia fracture plays an important role in accelerating the health recovery and relief to the patients.

Lidocaine is an amide local anesthetic that acts mainly through blocking the Sodium (Na⁺) channels and activating of several other cellular systems (Brunton *et al.*, 2011; Trevor *et al.*, 2015). Lidocaine with its anti-inflammatory effects attenuates inflammatory cytokines of interleukin B₁, interleukin 6 (IL 6) and anti-inflammatory cytokines and exerts its analgesic effects even at very low doses (Beilin *et al.*, 2003).

Systemic administration of lidocaine inhibits the arachidonic acid cascade, and the synthesis of eicosanoids and prostaglandins (Kuo *et al.*, 2006). In addition, it stimulates the smooth muscles of the bowel (Smith *et al.*, 1977). These inhibitory impulses are generated after the manipulation and the stimulation of the peritoneum during surgery. Therefore, Lidocaine infusion reduces ileus after surgery and causes better gas defecation in surgeries (Kaba *et al.*, 2007).

Acute postoperative pain is associated with various complications and high financial and health burdens in the healthcare system worldwide. In this regard, reducing the postoperative pain and its efficient management is always a priority in all types of surgeries. Because of low cost, easy to use, and relatively low side effects, lidocaine infusion during surgery may be an efficient and cost-effective option for control of acute postoperative pain (Mao & Chen, 2000; McCarthy *et al.*, 2010). Therefore, the present study was aimed to evaluate the analgesic effects of lidocaine infusion on the intensities of acute postoperative pain and on the amount of the postoperative opioid prescription in the patients underwent tibial fractures.

Methodology:

This was a randomized, double-blind controlled trial type of study conducted on the patients under treatment of tibial fracture type I or II in Imam Khomeini Hospital, Ahvaz, Iran. The protocol of the present study included the interventions, clinical assessments, and data collections from the anesthesiology department of the Hospital, which is affiliated to Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran. After the enrolment of all patients and before starting the study, researchers completely and clearly explained all objectives and protocols of the study and possible benefits and side effects of the treatments to all participants and got the consent of them for participation. Total 48 patients go

through the surgery of tibial fractures with the American Society of Anesthesiologists (ASA) classification of types I or II. The participants aged 18 to 50 yrs. with body mass index (BMI) ranging 18.5- 35 were randomly divided into treatment and control groups (each 24 patients). At the beginning of the referral to the operating room, a physician who was blind on the used drugs filled the questionnaire. The patients with the history of the kidney and the liver failure, seizure disorders, sensitivity to local anesthetic, chronic pain syndrome, those with an ASA classification of III and IV due to chronic disease, and chronic use of sedative drugs or opioid were excluded from the study. After routine monitoring, induction of anesthesia was conducted by 1mg Midazolam, 5 mg/kg 5 Sodium Thiopental (STP) of, 2 µg/kg Fentanyl and 0.5 mg/kg Atracurium. After an incubation period of the patients, controlled ventilation was applied by prescribing 50% NO₂ and 50% O₂. During operation, intravenous infusion of Remifentanyl was done with the dose of 0.1 µg/kg/min and Propofol with the dose of 100 µg/kg/min.

In the treatment group, intravenous lidocaine with the bolus dosage of 1.5 mg/kg was injected concurrently with the induction of anesthesia. During surgery, lidocaine infusion continued with the dose of 1.5 mg/kg/hrs and terminated at the end of the surgery. In the control group, normal saline was injected as an intravenous infusion.

The intensity of the postoperative pain was rated using 0 to 10 numerical visual analog scale at 1, 2, 4, 12, 16, 20, and 24 hours after the surgery. As zero was equal to no pain or analgesia and 10 was equal to the worst imagined pain for the patient. For the VAS<3, Diclofenac 100 mg suppository and for the VAS>3, intravenous 20 mg Pethidine was administered. In addition, the total prescribed opioid was recorded during the first 24 hours. During the experimental procedures, 2% lidocaine vial (Aboureihan Co., Iran) and 50 cc syringe (Azar Syringe Co., Iran) were used. For comparing the demographic data on age, weight, height, and the duration of the operation central tendency index was used. The data were expressed as mean±standard error of the mean (SEM) for all quantitative variables. The data were analyzed with statistical package SPSS (Windows, version 17).

Results:

Total 21 patients of the treatment group and 16 patients of the control group were men. The Chi-square test showed that the two groups were homogeneous on the distribution of gender. In addition, the t-test showed that the two groups did not significantly differ in terms of age, weight, and height.

The mean duration of anesthesia in the treatment and control groups were 85 and 73 min, respectively. The mean duration of the operation for the treatment and control groups were 70 and 60 min, respectively indicating no

Table-1: The demographic data and the results of the first time of analgesic request SEM; standard error of mean

Parameters	Treatment						Control						p value
	N	Mean	Med.	Min.	Max.	SEM	N	Mean	Med.	Min.	Max.	SEM	
Age (year)	24	25	23	18	45	2	24	25	22	18	48	2	0.922
Weight (kg)	24	73	70	60	90	2	24	72	73	52	92	2	0.632
Height(cm)	24	173	174	160	180	1	24	169	172	153	178	2	0.208
Duration of anesthesia	24	84	85	60	110	2	24	73	75	20	95	3	0.246
Duration of surgery	24	68	70	50	90	2	24	60	68	0	75	4	0.800
remifentanyl dose	24	433	400	330	600	18	24	398	400	300	500	11	0.032
propofol dose	24	321	325	200	500	19	24	379	400	250	450	10	0.020
First time of analgesic request	24	220	190	90	615	33	24	122	120	80	180	7	0.006
Pethidine dose	24	0	0	0	0	0	24	5	0	0	25	2	0.011

significant difference based on the 't'-test.

To evaluate the pain intensity a numerical rating scale of VAS was used separately for men and women using Mann-Whitney test. A comparison was done for the intervals of 1, 2, 4, 12, 16, 20, and 24 hours post-operation in men and women. The time of 2, 4, and 12 did not show a significant difference, but at other times, showed a significant difference.

Nevertheless, the first time of analgesic request after the end of the anesthesia for the treatment and control groups was found to be 220 and 120 min respectively which was significantly different between the two groups, $p < 0.006$ (Fig.-1).

The average pain scores for the treatment and control groups at the intervals of 1, 2, 4, 12, 16, 20, 24 hours of post-operation were respectively 1.6, 2.4, 2.2, 1.6, 1.4, 1.3, and 1.2 and 3.4, 3.2, 2.4, 1.8, 2.1, 2.5, and 1.8.

The average intensities of pain between the women and men at 2, 4, and 12 hours after the surgery did not show any significant difference. However, at other intervals, the median of the pain in the group receiving lidocaine is lower than the control group ($p < 0.01$) (Fig.-2).

The mean of the total used dosages of the opioid (pethidine) during the first 24 hours after surgery in the treatment and control groups were 0 mg and 125 mg, respectively.

Evaluating the first time of analgesic request from the end of the anesthesia (in minutes) shows that the patients in the treatment group had their first analgesic request at the mean time of 220 min, compared with the mean time of 120 min in the control group that was significantly

Figure-1: The comparison of the mean time for the first analgesic request between the two groups

Error Bars +/- 1 SE

Figure-2: The comparison of the pain intensity variations over time of post-operation between the two sexes

different between the two groups ($p < 0.006$).

Discussion:

The results of our study show that intravenous infusion of lidocaine during surgery relatively reduces postoperative pain in the patients faced tibial fracture. In addition, the amount of the prescribed opioid drug the first 24 hours after operation in the patients receiving lidocaine was less than those receiving placebo. Moreover, receiving lidocaine delayed the first time of the analgesic request from patients. On the other hand, intravenous infusion of lidocaine with the distinct prescribed dosage during surgery does not impose any side effects during and after the operation. Harvey *et al.* (2009) conducted a study on 22 patients candidate for elective abdominal surgeries (Bowel) in America, under the same conditions as our study. The difference with our study was the continuance of lidocaine infusion for 24 hours post-operation. They reported a significant reduction of the pain in the treatment group, compared to the control group who received normal saline.

Martin *et al.* (2008) found that the low dose infusion of lidocaine during surgery in total hip operations was not effective in inhibiting pain after surgery. Koppert *et al.* (2004) conducted a similar type of study on 40 patients undergoing major abdominal surgery. The pain intensity after the operation was evaluated using the numeral rating scale and taking morphine until 72 hours after surgery. The patients who received lidocaine had lower pain and needed less morphine during 72 hours after the operation.

RESEARCH ARTICLE

In another relevant type of study conducted on 67 ambulatory patients aged between 18 to 75 years old with an ASA- classification of I, II and III, the rate of postoperative pain during 48 hours after surgery showed a significant reduction, whereas the time for the release of ambulatory patients did not significantly changed (Mc Kay *et al.*, 2009). The main differences of our findings with the other relevant studies were the site of surgery and the long-lasting effects of the lidocaine on the pain reduction. However, most of the previous studies were based on the major abdominal and thoracic surgeries. Moreover, the analgesic effects of lidocaine remained significant at the second and third days after the operation. The main limitation of this study was the relatively short follow-up of 24 hours and we did not assess the analgesic effects of lidocaine beyond the 24 hours post-operation. Furthermore, as the measurement of the blood level of lidocaine was not possible, we only used lidocaine infusion with the standard dosage in our study. Conducting randomized controlled studies with big sample size can shed more lights on the effects of lidocaine in postoperative pain in different surgeries and reducing the side effects and costs of the surgeries.

Acknowledgment:

The authors of this study would like to thank Vahid Salehi, Dr. Marzieh Ghasemi and all other persons who assisted us in conducting this study.

References:

- Akhondzadeh, R., Nesioonpour, S., Gousheh, M., Soltani, F. & Davarimogadam, M. (2017): The Effect of Magnesium Sulfate on Postoperative Pain in Upper Limb Surgeries by Supraclavicular Block Under Ultrasound Guidance. *Anesth. Pain Med.*, 7(3):e14232.
- Ballantyne, J.C., (2006): **The Massachusetts General Hospital Handbook of Pain Management Philadelphia**: Pub. by: Lippincott Williams & Wilkins Handbook. 628 p.
- Beilin, B., Bessler, H., Mayburd, E., Smirnov, G., Dekel, A., Yardeni, I. & Shavit, Y. (2003): Effects of Preemptive Analgesia on Pain and Cytokine Production in the Postoperative Period. *Anesthesiology*, 98(1):151-155.
- Block, B.M., Liu, S.S., Rowlingson, A.J., Cowan, A.R., Cowan Jr, J.A. & Wu, C.L. (2003): Efficacy of postoperative epidural analgesia: a meta-analysis. *Jama*, 290(18):2455-2463.
- Brown, A.K., Christo, P.J., & Wu, C.L. (2004): Strategies for postoperative pain management. *Best Prac. Res. Clin. Anaes.*, 18(4): 703-717.
- Brunton, L.L., Chabner, B.A. & Knollman, B.C. (2011): **Goodman and Gilman's The Pharmacological Basis of Therapeutics**. 12th ed. Pub. by: McGraw-Hill Education. 1808 p.
- Fishman, S.M., Ballantyne, J.C. & Rathmell, J.P. (2010): **Bonica's Management of Pain** 4th ed. Pub. by: Philadelphia, Wolters Kluwer/Lippincott, Williams and Wilkins; 2064 p.
- Harvey, K., Adair, J., Isho, M. & Robinson, R. (2009): Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in elective bowel surgery? A pilot study and literature review. *Am. J. Surg.*, 198(2):231-236.
- Kaba, A., Laurent, S.R., Detroz, B.J., Sessler, D.I., Durieux, M.E., Lamy, M.L. & Joris, J.L. (2007): Intravenous Lidocaine Infusion Facilitates Acute Rehabilitation after Laparoscopic Colectomy. *Anesthesiology*, 106(1):11-18.
- Kasper, D., Fauci, A., Hauser, S., Longo, D., Jameson, J., & Loscalzo, J. (2015): **Harrison's Principles of Internal Medicine**, 19ed. Pub. by: McGraw-Hill Education.
- Kehlet, H., & Wilmore, D.W. (2002): Multimodal strategies to improve surgical outcome. *Am. J. Surg.*, 183(6):630-641.
- Koppert, W., Weigand, M., Neumann, F., Sittl, R., Schuettler, J., Schmelz, M. & Hering, W. (2004): Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. *Anesth. Analg.*, 98(4):1050-1055.
- Kuo, C.P., Jao, S.W., Chen, K.M., Wong, C.S., Yeh, C.C., Sheen, M.J. & Wu, C.T. (2006): Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br. J. Anaesth.*, 97(5):640-646.
- Martin, F., Cherif, K., Gentili, M.E., Enel, D., Abe, E., Alvarez, J.C., Mazoit, J.X., Chauvin, M., Bouhassira, D. & Fletcher, D. (2008): Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. *Anesthesiology*, 109(1):118-123.
- Mao, J., & Chen, L.L. (2000): Systemic lidocaine for neuropathic pain relief. *Pain*, 87(1): 7-17.
- McCarthy, G.C., Megalla, S.A., & Habib, A.S. (2010): Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery. *Drugs*, 70(9): 1149-116
- McKay, A., Gottschalk, A., Ploppa, A., Durieux, M.E. & Groves, D.S. (2009): Systemic Lidocaine Decreased the Perioperative Opioid Analgesic Requirements but Failed to Reduce Discharge Time After Ambulatory Surgery. *Anesth. Analg.*, 109(6):1805-1808.
- Nesioonpour, S., Akhondzadeh, R., Mokmeli, S., Moosavi, S., Mackie, M. & Naderan, M. (2014): Does low-level laser therapy enhance the efficacy of intravenous regional anesthesia? *Pain Res. Manag.*, 19(6):e154-e158.
- Smith, J., Kelly, K.A. & Weinshilboum, R.M. (1977): Pathophysiology of Postoperative Ileus. *Arch. Surg.*, 112(2):203-209.
- Trevor, A.J., Katzung, B.G., Masters S, Knudering-Hall, M. (2015): **Katzung & Trevor's Pharmacology: Examination & Board Review**, 11th ed. Pub. by: McGraw-Hill Education. 456 p.