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Local Anesthetic Effect of Amitriptyline versus Lidocaine in Isolated Lesion of the Limb Requiring Primary Suturing; Assessing a Novel Therapeutic Agent

***Rasoul Salimi*[1*], *Rasool Haddadi*[2,3], *Abbas Moradi*[4], *Farnoush Jalilvand*[1], *Farzin Firozian*[5]**

[1]*Department of Emergency Medicine, Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran*
[2]*Department of Pharmacology, Faculty of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran*
[3]*Medical Plants And Natural Products Research Center, Hamadan University Of Medical Sciences, Hamadan, Iran*
[4]*Department* of Social Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[5]*Department of Pharmaceutics, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran*

***Corresponding author:** *Rasoul Salimi*
Address: Shahid Beheshti Boulevard, Besat Hospital, Emergency Department, Hamadan, Iran. **Tel:** +98-81-32640020, **Fax:** +98-81-32640020
e-mail: rasoulsl@yahoo.com

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ABSTRACT

Objective: To compare the anesthetic effects of topical amitriptyline 2% with lidocaine 2% in isolated limb wound repair with suturing.
Methods: In a randomized clinical trial, 90 patients with a complaint of isolated ulcer and require a preliminary repair by suturing were selected from patients referred to emergency department of Beast Hospital in Hamadan. First, the scars were washed and anesthetized with lidocaine 2%. If after the peak period effect of lidocaine, the pain score of patients did not decrease, they randomly assigned to two groups, Lidocaine or Amitriptyline gel. After the intervention and during the suturing, the patient's pain score was measured at the intervals specified time by the visual analogous scale (VAS) and results recorded on the checklist. Finally, the collected data were analyzed by SPSS software version 20 at 95% confidence level
Results: In the lidocaine and amitriptyline group, the mean age of the patients was 29.08 and 27.34 years, and male gender frequency was 71.1% and 80% respectively. Both groups were matched for age and sex. Mean score of pain in both groups decreased from the score of 10 before the intervention to 7.33 in the lidocaine group and 0.53 in amitriptyline group. Based on the results of the ANOVA repeated measure test, there was a statistically significant difference between the mean score of pain in the two groups (p<0.001).
Conclusion: In patients with isolated limbs ulcers, requiring initial repair with suturing, numbness and analgesia effect of amitriptyline 2% gel, with dose 2 mg/kg is better than lidocaine 2%.
Clinical Trial Registry: IRCT20120215009014N216

Keywords: Anesthetics; Amitriptyline; Lidocaine; Wounds and injuries.

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Introduction

Pain is an unpleasant sensation and a sensory experience that is associated with actual damage or possible damage to the tissue, or is justified by such damages. Postoperative pain is an important issue for the patient and the surgeon [1]. It is preferred to use methods that minimize postoperative pain and disability. The main mechanism of the effect of anesthetics is the inhibition of neuronal transmission through the reversible blockage of sodium channels [2]. The flow of sodium in the membrane of the nerve cells is essential for the cellular depolarization of the cell and consequently for the passage of the nerve wave [3, 4]. When the nerve loses its depolarization property, its nervous impulses are not transmitted.

Tricyclic antidepressants (TCA) have extensive peripheral and central effects. It has been shown that amitriptyline and desipramine produce analgesic effects in animals following the pain caused by formalin in animals [5, 6]. Some amitriptyline antinociceptive effects appear to be applied through adenosine receptors [7]. Local anesthetic drugs with an obstruction of sodium channels cause numbness and antinociceptive effects of TCA drugs have been demonstrated systemically and even topical administration, such as doxepin, and also showed that TCA such as amitriptyline is reluctant to attach to the same position of anesthetics at the surface of the sodium channel, in other words, the amitriptyline receptor overlaps with anesthetics in the sodium channel.

Amitriptyline is a class of tricyclic drugs that is known as an antidepressant drug, but it also has other uses. It was first used in 1977 for the treatment of patients with diabetic neuropathy. This effect is also independent of the effects of anti-depressants [8, 9]. This effect has been seen in the form of the administration of amitriptyline orally. A lot of studies have been done on the mechanism of antinociceptive effect of amitriptyline. Strengthening the analgesic effect of morphine and endogenous opioids, the inhibition of noradrenaline and serotonin reuptake and the control of NMDA receptors and 5-HT3 receptors in the central levels have been reported. In relation to the mechanism of the effect of amitriptyline on the peripheral level, it has been shown that the drug can causes analgesia by inhibiting direct discharges of peripheral sensory fibers and, by reducing inflammatory activity in the environment. Other evidence has been reported that sodium channel has been inhibited by this drug. Also, amitriptyline blocks the Na flows into the heart cells [10]. According to the results of studies that have proved the evidence of the antinociceptive effects of amitriptyline, the present study aimed to compare the effect of amitriptyline antinociceptive effects and Lidocaine for the lesions of the limb requiring primary suturing.

Materials and Methods

Study Population

This study was a randomized clinical trial (Randomized Clinical Trial). The project was approved by the Clinical Research Ethical Committee of Hamadan University of Medical Sciences. *The study Registry's Code* of *Ethics was* IR.UMSHA.REC.1396.811 and the clinical trial registry code was IRCT20120215009014N216. The patients referred to the emergency department of Besat Hospital of Hamadan- Iran, who met the study inclusion criteria were evaluated by convenience sampling. Patients with isolated, superficial skin lesions requiring primary suture repair were selected.

Preparation of 2% Amitriptyline Gel

180 mg of methylparaben and 20 mg of propylparaben were dissolved in 74 ml of water at 70 °C. Then, 300 milligrams of Carbopol®*940* were added slowly while stirring with a homogenizer. 2 g of the amitriptyline was added to the final suspension. 2 ml of sodium hydroxide 10% *wt/wt* added to the suspension to form the gel. 1.5 g of *K30 (Kollidon*® 30*)* was dissolved in 20 ml of water and added to the gel.

Intervention

After wiping the wound, all patients underwent anesthesia with lidocaine 2% at 3 mg/kg body weight. If after a peak period of lidocaine (3 minutes) with a VAS score, the pain score was less than three, the wound was restored and the patient excluded. However, if the pain was low but still painful (score of 8 and above), they were assigned to the treatment groups of the topical gel of lidocaine 2% (2 mg/kg body weight) or 2% amitriptyline gel (at 2 mg/kg body weight) by a balanced (permuted) block randomization. In order to blind the study, the drugs were given to the nurse in a single-shaped syringe with a volume equal to A and B. The person who injected the drug and the person who evaluated the pain score were not aware of the contents of the syringes; the codes were given to the statistician during the analysis. After the intervention and during suturing, the pain score of the patients was evaluated at the first, third, fifth, seventh and ninth minutes, and the results were recorded on the checklist. Criteria for inclusion in the study include: Patients with isolated superficial skin lesions requiring primary suturing repair, ages 18 to 60 years, lack of history of use of Monoamine oxidase inhibitors (MOAI), absence of cardiovascular disease, and patient satisfaction for participation in the study. Patients with active arterial hemorrhage or unstable vital signs were excluded from our study. A checklist for registering patients' demographic characteristics and Visual Analogue Scale (*VAS*) was used to assess the pain.

Statistical Analysis

Sample size was calculate based on previous trials. The final data analyzed using SPSS software (version 20). In order to describe the data measures of *central* tendency (mean and median), dispersion indexes (standard deviation) and frequency were used. For comparing the gender difference and two study groups of Lidocaine 2% and 2% amitriptyline Chi-square test was used. The mean differences were compared using t-student test in some cases. In order to compare the mean score of pain in patients at each assessment stage, due to the non-normality of the distribution of data (based on the Kolmogorov-Smirnov test), the Mann-Whitney non-parametric test was used. Moreover, repeated measure ANOVA was used for evaluating and comparing of mean differences of the patient pain score totally. *P*-value less than 0.05 considered statistically significant.

Results

In this study, 90 patients who referred to emergency department of Besat Hospital of Hamadan with a complaint of isolated superficial lesions and needing initial suture repair were examined. They were randomly assigned to two groups of 45 patients (Figure 1). For gender in the lidocaine group, the number of males and females were 32 (71.1%) and 13 (28.9%), and 36 (80%) and 9 (20%) in the amitriptyline group. respectively. Based on the Chi-square test, 95% confidence interval the differences between the two groups was not statistically significant in gender (p=0.32).

The groups were identical in terms of sex. The mean age of the patients in the lidocaine group was 29.08±12.41 years, and ranged between at least 3 and at most 59 years. The mean age in the amitriptyline group was 27.34±17.61 years. According to the results of t-test, there was no statistically significant difference was seen for age between the two treatment groups (p=0.58).

Results of Mann-Whitney non-parametric test showed that, there was no statistically significant difference between the mean scores of pain in two study groups before the intervention. But from the first to the fifteenth minute after intervention, the mean pain score in the amitriptyline group decreased significantly compared to the lidocaine group (p<0.001) (Table 1). ANOVA test results revealed a significant difference between the pain score in the study groups (p<0.005). In order to evaluate the tangible time of pain relief compared to other times, the *Bonferroni correction test was performed*, which showed that the pain score of patients at all measuring times was significantly lower than the previous time in the amitriptyline group (p<0.001), but in the lidocaine group, the pain score was significantly decreased from the fifth minute afterwards (p<0.001) (Figure 2).

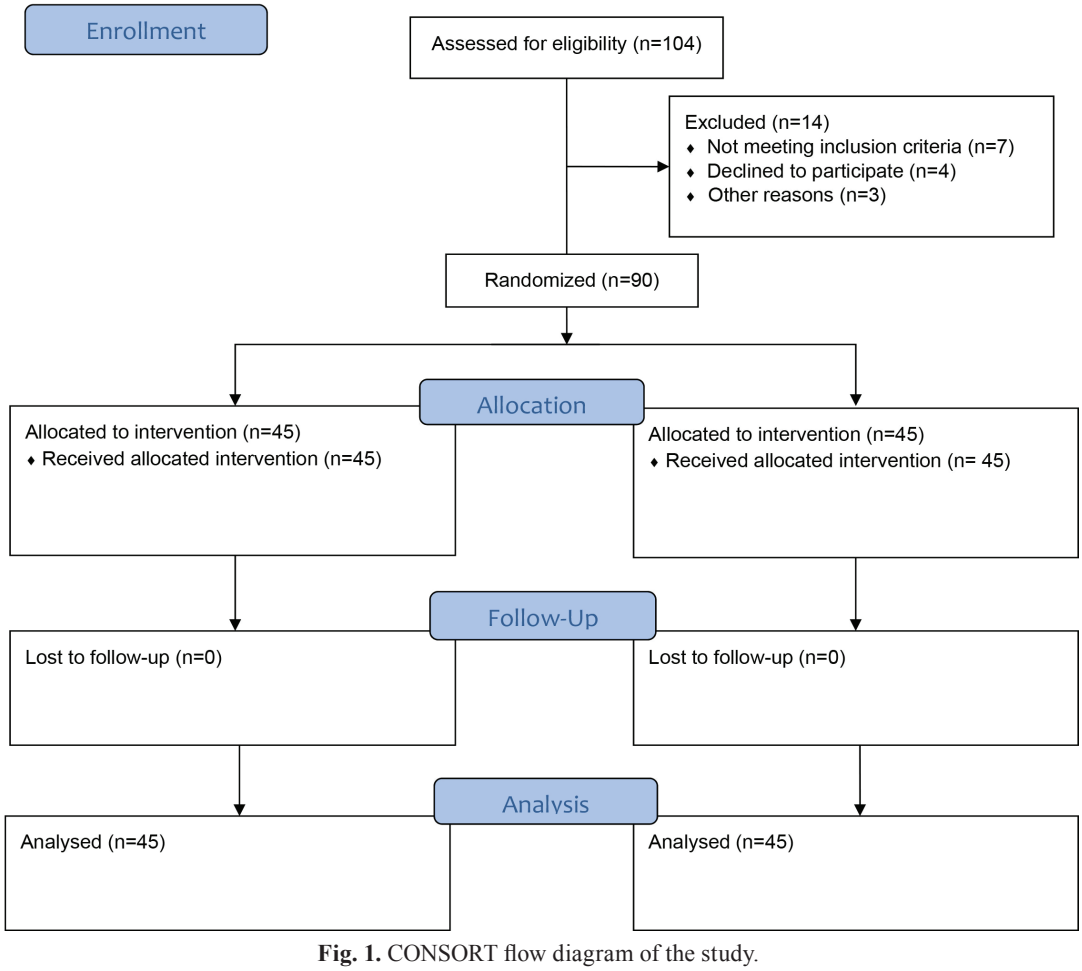

Fig. 1. CONSORT flow diagram of the study.

Table 1. Comparison of mean pain score of patients in terms of study group in different periods

Time	Study groups		*p* value[a]
	Amitriptyline (N=45)	Lidocaine (N=45)	
Before intervention	10.0±0.0	10.0±0.0	0.998
Fist minute	8.62±0.94	10.0±0.0	<0.001
3rd minute	7.22±1.46	9.82±0.58	<0.001
5th minute	5.78±1.36	9.11±1.0	<0.001
7th minute	4.40±1.51	8.13±0.89	<0.001
9th minute	2.89±1.45	7.64±0.88	<0.001
15th minute	0.53±1.31	7.33±1.13	<0.001

[a] Mann-Whitney U test

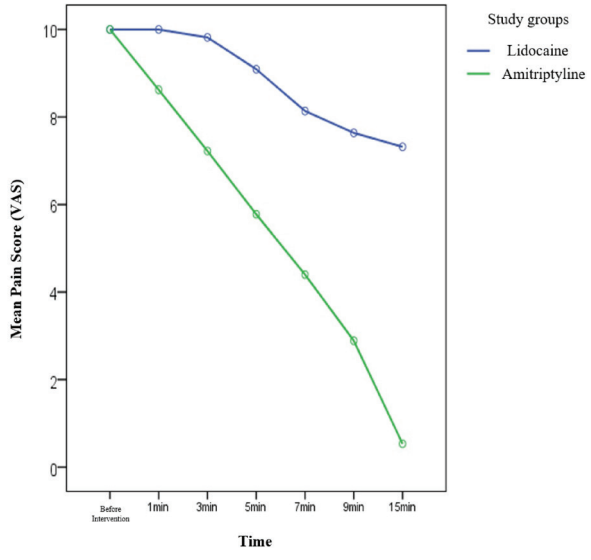

Fig. 2. Changes in pain score in patients over the different study periods.

Discussion

This maybe the first report of amitriptyline inducing anesthesia of the skin wounds when applied in human. Although lidocaine products have various applications such as for diabetic neuropathies, fibromyalgia and etc. routinely [5-8]. Based on the findings of the present study, the patients in the Lidocaine and intervention (Amitriptyline) groups were matched for age, sex and pain score before intervention. From the first to the fifteenth minutes' post-intervention, the mean score of pain in the intervention group was significantly lower than the Lidocaine group. Also there was a significant difference between the pain score in the two study participants.

The exact mechanism of amitriptyline causing local anesthesia of the skin is not specified yet and does not fall within the scope of this article. We surmise that, multiple *mechanisms* of action contribute to the analgesic and anesthetic effect of effects amitriptyline are existed which the most important of them include Na^+ and Ca^+ channel blockade, and block of histamine, cholinergic, and α-adrenergic receptors [1, 8, 9]. One of the few studies conducted on the use of amitriptyline in humans was the study of Moghadamnia *et al*., [11] which investigated the local anesthetic effect of amitriptyline gel in the inflamed pulp teeth. In this clinical trial study, patients who continued to have pain despite local anesthesia during creating an endodontic cavity, were treated with a special 0.2 ml syringe of amitriptyline gel, and the other group received placebo gel. The results of the study showed that amitriptyline gel significantly increased the local anesthetics effects compared to the placebo. The effect of topical amitriptyline 2% and ketamine 1% on the treatment of neuropathic pain syndrome in patients with diabetic neuropathic pain were also studied by Mary *et al*., [12] No significant differences in pain and symptoms of the patients were reported.

In contrast, some studies indicated the effective role of topical combination of ketamine-amitriptyline in pain relief for rectal and genital pain [13]. Uzaraga *et al*., [14] compared the effects of the combination of amitriptyline and lidocaine with ketamine and placebo in the treatment of neuropathic pain caused by skin reaction to radiotherapy. The follow-up results of patients over a 14-month period showed that pain, burning and local stimulation were significantly less in the intervention group than the control.

The results of the present study were in line with the findings of the above observations, so that the topical use of 2% amitriptyline gel significantly reduced the pain of the isolated wounds of the limb during the initial repair with the sutures, as well as the analgesic effect of the amitriptyline was higher than lidocaine.

The impossibility of depriving patients of the routinely used local anesthetic drugs in the hospital was one of the limitations of the study in terms of ethical issues which can interfere with the interpretation of pain score in patients. From the strengths of this study, the presence of external control group and random allocation of patients that were divided into two treatment groups. It is recommended that amitriptyline 4% and 6 % with fat-soluble compounds be used in the future studies, to be more effective. It is also suggested to use of lidocaine gel in the wounds of other parts of the body that have no active bleeding, without Lidocaine injection.

In general, it can be concluded that the antidepressant amitriptyline, often used for the management of pain as oral for various indications, has the potential to be used locally to induce anesthesia in human skin more effective that the current drugs. This effect is

better achieved with 2% gel form of amitriptyline with the dose of 2 mg/kg.

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Conflicts of Interest: None declared.

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