Pharmaceutical Sciences
September 2019, 25(3), 177-183
doi: 10.15171/PS.2019.48
https://ps.tbzmed.ac.ir/

Review Article

Use of Lidocaine for Pain Management in the Emergency Medicine: A Systematic Review and Meta-Analysis

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Article Info

Article History:
Received: 14 April 2019
Revised: 31 May 2019
Accepted: 29 June 2019
ePublished: 30 September 2019

Keywords:
-Lidocaine
-Pain management
-Emergency medicine

ABSTRACT

Background: Lidocaine is a well-known medium-acting local anesthetic with a short onset time. It is a valuable drug for managing both acute and chronic pains and is being used as a popular agent for pain control in the emergency department (ED). In this systematic review, we intended to define the effectiveness of lidocaine in pain management of the patients referring to ED.

Methods: The preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement was utilized for this Systematic Review (SR). We searched the databases of PubMed, Scopus, ProQuest, and Medline (Ovid) from 1990 to August 2017 for Randomized Controlled Trials (RCTs) in which the study population was referred to the emergency department and received lidocaine. Full-texts of the studies that were published in English were reviewed for inclusion. Both authors individualistically evaluated all studies. Seven articles were eligible for the meta-analysis based on their common outcomes.

Results: The total number of subjects was 671. The studies were categorized based on the type of drug and administration route. Mean pain, regardless of the drug administration method, in the placebo group was 0.69 units higher than the lidocaine group. Considering the administration route, mean pain in the placebo group was 0.35 units higher than the lidocaine group when administered topically, and it was lower in the subcutaneous method than the topical method by 1.41 units.

Conclusion: Infiltration of lidocaine decreases pain of different procedures in the ED whereas the effect of topical lidocaine is controversial issue.

Introduction

Pain management is one of the main priorities in the emergency department (ED) and sedation of the patient is a way to calm him/her down. The mechanism of local anesthetic drugs is to prevent the onset of impulse transmission along the axon. This process is performed by blocking the voltage-dependent sodium channels. Local anesthetic agents are divided into two groups: 1. Amino esters 2. Amino amides. Amino ester agents are metabolized by plasma esterase, and amino amide agents in the liver by hepatic enzymes.[1] Lidocaine, the most effective local anesthetic, is in the amide group. It is a well-known medium-acting local anesthetic drug with a short onset of action time. It is not only a valuable drug for controlling neuropathic pain, but also for managing both acute and chronic pains[2] and is also used as an anti-arrhythmic drug. Since 1980, its intravenous administration has been used as a diagnostic tool in some cases, as well as a therapeutic tool for treatment of severe neuropathic pain. Moreover, it is used for management of chronic pains due to neurological diseases causing myofascial pain, stroke, and neurogenic facial pain. As a result, 78% of patients receiving intravenous lidocaine had a positive result.[3] Reports of such randomized controlled trials (RCTs) has made lidocaine a popular agent for pain control in the Emergency Department (ED) and we aimed to determine its analgesic effects in patients admitted to the ED in a systematic review of RCTs. This study reports the effectiveness of lidocaine in pain management of the patients referring to emergency setting and can provide clinical evidence for ED physicians.

Materials and Methods

Study protocol

A systematic review (SR) of databases was conducted to find RCTs investigating the effect of lidocaine in

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management of pain in the ED. The PRISMA statement was utilized for this SR. Searching databases, selecting studies, evaluating the quality of studies, and extracting data were done by two researchers. Whenever there was a discrepancy between two researchers, the subject was consulted and considered by a thir d reviewer.

Inclusion and Exclusion Criteria

Inclusion criteria for the studies were as following: 1. RCTs investigating the effect of lidocaine in management of pain in the ED; 2. Articles in which the study population was referred to the emergency department; 3. Studies in which the patients received lidocaine; the articles published from 1990 to August 2017; 4. Articles published in English. Exclusion Criteria were as following: 1. Articles in any language other than English; 2. Articles with low quality; 3. Articles conducted in animals; 4. Qualitative articles; 5. Articles without complete information; 6. Review articles, case reports and letters to the editor; 7. Articles published before 1990.

Information databases and search strategy

We searched the databases of PubMed, Scopus, ProQuest, Medline (Ovid). Keywords selection was done based on Mesh terms using OR and AND operators and included emergency medicine, emergency department, emergency service, lidocaine, lingocaine, xyloneural, 2-2etn-2mephacn, 2- (diethyl amino) -n- (2,6-dimethylphenyl) acetamide, octocaine, xylicaine, xylocytine, daltcine, pain management, pain relief, pain control, visual analog scale, numeric pain rating scale, local anesthesia, local anesthetic, intravenous anesthetic. Correlated references of the selected studies were searched manually. Gray literature and studies which were presented at conferences were also searched. Subject-matter experts were communicated to gather information about published and non-published studies.

Selection of studies and data extraction

Articles which were extracted from the databases by the aforementioned keywords were chosen in 3 steps by subject specialist. Firstly, the titles of all articles were reviewed and articles that were not relevant to the aims of the study were excluded. The abstract and the full text of the articles were studied and studies with exclusion criteria and poor association with the study objectives were identified and abandoned. Selected studies were assessed for bias risk by two evaluators using the Cochrane checklist and the discrepancies between the two evaluators were referred to the third person and eventually entered the RevMan software version 5.3.

The information extracted from the articles was summarized in the data extraction form including: first author, year of publication, country of study, type of interventions, number of people in the control and intervention group, type of study, and mean age of patients in each group. The EndNote X5 Resources Management Software was utilized for categorizing, studying the titles and abstracts, besides identifying duplicate cases.

Statistical analysis

The number of subjects, mean (standard deviation) of pain in each group was extracted from the articles. The mean difference of pain was calculated for each study. Meta-analysis was used to combine the results. The heterogeneity between studies was investigated by Cochrane (Q) and I2 statistics, which express the percentage of variations between studies. I2 values less than 25% specify low heterogeneity, between 25% and 75% identify average heterogeneity and over 75% show high heterogeneity. In the case of heterogeneity, the random effects model was utilized to estimate the overall effect size. The funnel plot and Egger regression tests were utilized to evaluate the publication bias. Statistical analysis was done by CMA v.2.0 software. P-value lower than 0.05 was considered the meaningful level.

Table 1. Characteristics of included studies.

	Country	**Study Type**	**Drug**	
			Group A	**Group B**
Şener A. *et al* (2015)	Turkey	Randomized prospective	Lidocaine hydrochloride 2%	Lidocaine hydrochloride 2%
Jenkins M. *et al*. (2014)	Ireland	Open labeled Non-Inferiority Randomized Controlled Trial	Lidocaine infiltration (1% w/v)	Topical anesthetic putty (containing 4.94% w/w lidocaine hydrochloride, equivalent to 4% w/w lidocaine base
Chale S. *et al*. (2006)	USA	Randomized controlled trial	Lidocaine1%	Lidocaine1%
Brenner S. *et al*. (2012)	USA	Prospective, randomized, double-blind, placebo control	Placebo cream	Liposomal 4% lidocaine
Hajiseyedjavady H. *et al*.(2011)	Iran	Randomized controlled clinical trial	0.2 mL of lidocaine 2%	1 mL of lidocaine gel 2%
Valdovinos NC. *et al*. (2009)	USA	Prospective, placebo-controlled, double-blind study	LMX-4 cream (4% concentration of lidocaine and 1.5% concentration of benzyl alcohol as a preservative)	Placebo (water (purified), glycerin, stearylalcohol,stearic acid, sodium stearyl sulfate, methyl paraben, propyl paraben, dilauryl thiodipropionate, and sodium sulfate)
Harris T. *et al*. (2001)	Australia	Clinical trial	Lidocaine 1%	Saline

Results

Articles characteristics

A systematic search of databases was conducted and 374 titles were found, two individuals selected 131 titles for the original review (11 titles were deleted as they were duplicated). Sixty-eight articles were excluded as they were not RCTs. Twenty-four articles were excluded due to unavailability to their full texts. Extraction table was organized based on the outcomes of each study and common outcomes were ultimately collected. Thirty-two studies were excluded from the table as they did not have a mutual result. Finally, 7 articles were studied. The graph of the articles which were identified and studied are shown in Figure 1. The features of the studies are revealed in Table 1 and 2.

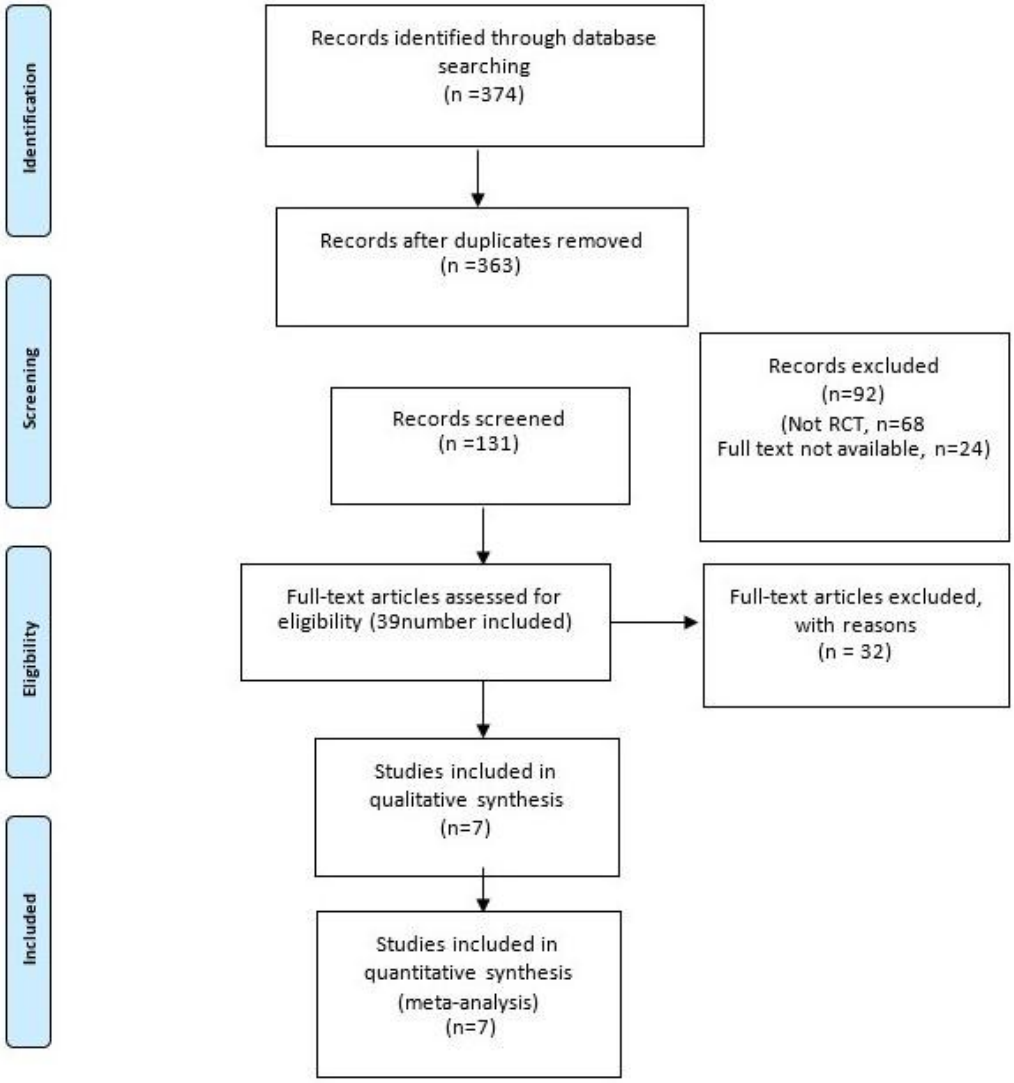

Figure 1. Flow diagram of trials for inclusion in the systematic review.
RCT: randomized control trial

Table 2. Characteristics of included studies (cont.).

Author	method		Age		Sample Size		Measurement
	Group A	Group B	Group A	Group B	Group A	Group B	
			Mean	Mean			
Şener A. *et al* (2015)	LIA	PNB	32±10.3	35±12.2	23	31	VAS
Jenkins M. *et al* (2014)	injection	topical	35(18-84)	35(20-81)	56	54	VAS
Chale S. *et al* (2006)	injection	injection	40.1±19.3	36.3±14.0	28	27	VAS
Brenner S. *et al* (2012)	topical	topical			57	57	VAS
Hajiseyedjavady H. *et al* (2011)	jet injection	topical	50.9±20.66	58.62±19.15	21	21	VAS
Valdovinos NC. *et al* (2009)	topical	topical	35±10	35±10	43	43	VAS
Harris T. *et al* (2001)	injection	injection			105	105	VAS

LIA: Local Infiltration Anesthesia
PNB: Peripheral Nerve Block
VAS: Visual Analog Scale

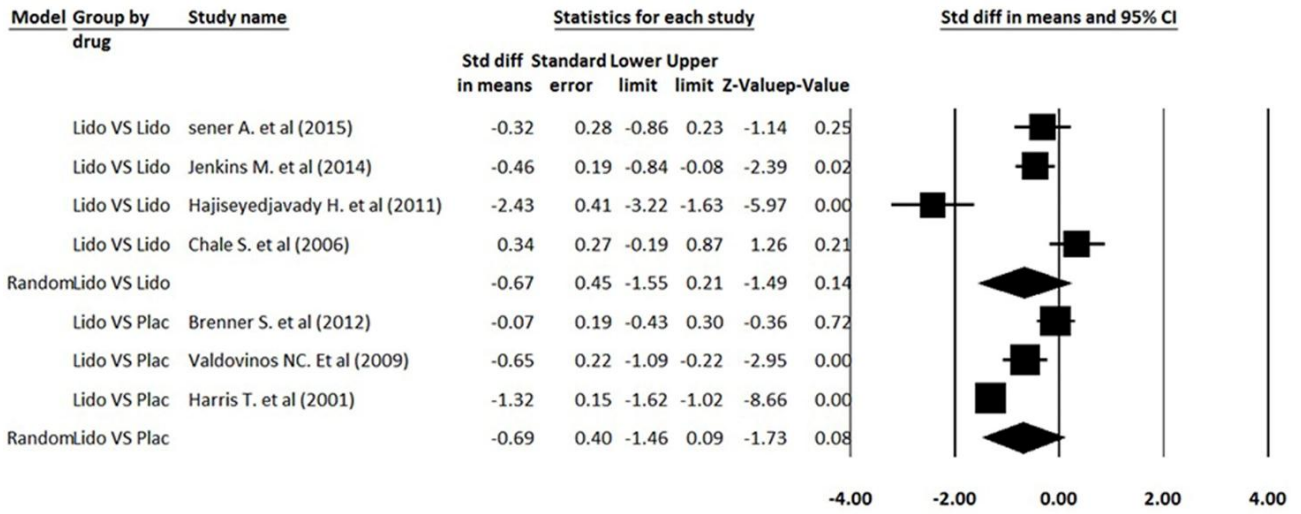

Figure 2. Quality of the articles based on the type of drugs.

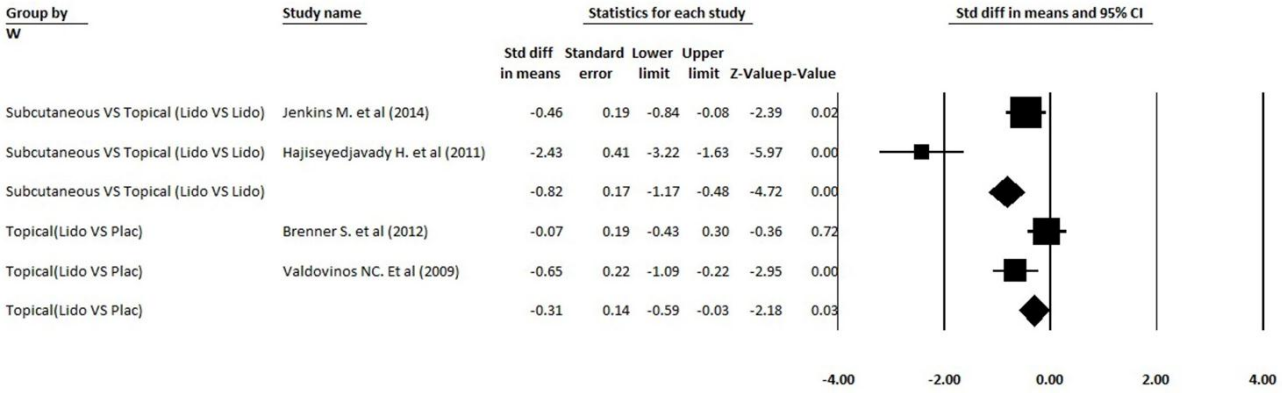

Figure 3. Quality of the articles based on the administration routes.

Quality evaluation of the articles

Criteria for evaluating the risk of bias in the Cochrane checklist included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and any other bias. Figure 2 and 3 demonstrates the results of the assessment of the quality of articles which entered this meta-analysis using the Cochrane tool. The word "yes" means a low risk of bias, the word "no" means a high risk of bias and the term "unclear" means that there is not adequate information to evaluate the risk of bias.

Meta-analysis

Following the review of the chosen articles, 7 articles were authorized for meta-analysis. The whole quantity of subjects was 671. The studies were categorized based on the type of drug and administration route, then analyzes were performed in each subgroup. Based on the results of the meta-analysis with the random effects model, the mean pain during manipulation, regardless of the drug administration method, in the placebo group was 0.69 units higher than the lidocaine group (Mean Difference= -0.69, n=3, SD= 0.40, P-value=0.08, I^2=92.68). In another analysis, considering the administration method, in the topical method, the mean pain during the manipulation in the placebo group was 0.35 units higher than the lidocaine group (Mean Difference=-0.35, n=2, SD=0.29, P-value=0.24, I^2=75.58), as well as the mean pain in the subcutaneous method was lower than the topical method by 1.41 units (Mean Difference= -1.41, n=2, SD=0.98, P-value=0.15, I^2=94.75).

Injection of lidocaine

A survey compared Lidocaine 2% hydrochloride for local infiltration anaesthesia (LIA) and peripheral nerve block (PNB) in repairing hand lacerations. Pain following injection was 24.5 and 29.7 for ILA and PNB, respectively. Pain during suturing was 5.6 for LIA and 9.2 for PNB, with no statistically significant difference. Four out of 54 patients needed repeated anaesthesia, one of which had received LIA. There was not a meaningful difference between two groups. Complete satisfaction was reported in 65.2% of patients who had LIA with Lidocaine hydrochloride and 58.1% of those who had PNB. Pinprick sensation was also evaluated in the mentioned study and time to loss of this sensation was reported. There was a statistically meaningful difference

between patients who had received LIA and PNB, time was longer in patients who received LIA.[4]

A study that compared analgesic effect of local or digital block of finger concluded that local administration of lidocaine 1% for wound anaesthesia omitted need for rescue anaesthesia. Pain caused by needle insertion, infiltration of lidocaine and suturing after local anaesthesia or digital block in finger did not differ in the study.[5] The effect of subcutaneous lidocaine injection prior to cannulation was studied by Harris *et al.* in 3 distinct groups of patients. In their study, 105 out of 366 patients received lidocaine and they were compared with 105 and 112 who received saline injection and no injection respectively. Pain score was noticeably lower using Kurskal-Wallis test ($p<0.0001$). Comparison of two control groups did not reveal any significant difference. Number of cannulation attempts did not significantly vary in these three groups.[6]

Lidocaine used for wound anaesthesia was evaluated in three studies, two of which compared its local administration with peripheral and digital nerve block. Its anaesthetic effect for finger did not differ when administered locally or used for digital nerve block, but when local administration was compared with peripheral nerve block, its local administration had more analgesic effect. Pain score and wound results after lidocaine administration were surveyed in the third study. The other study concluded that subcutaneous administration of lidocaine alleviated pain substantially.

Injection versus topical

According to a survey which evaluated local administration of lidocaine, mean visual analogue scale was 0.78 immediately after administration. When topical lidocaine was applied, mean pain score was 1.49. There was a significant difference in mean pain score which demonstrated that the efficacy of topical lidocaine was not lower than injection form. The maximum pain score was 5 for patients who had lidocaine injection and 7 in those who received it topically. After 7-10 days, five out of 43 patients had wound evaluation score of less than 6 in injection lidocaine group and 12 in the group receiving the drug topically. This valid score evaluates six items including presence of step-off, edge separation, counter irregularities, considerable distortion, margin inversion, and general cosmetic appearance. Side effects of topical and infiltration of lidocaine were equal. The number of patients who experienced wound infection was 4. Only one of the patients in whom lidocaine was infiltrated and one who received topical form needed resuturing. Repeated anaesthesia was required in 3 patients who had infiltration and 4 in topical anaesthesia group. Wound infection was reported in patients who had received injection of lidocaine and 2 in those who received topical anaesthesia. Wound separation was seen in 2 patients with topical administration. Wound inflammation was seen in only one patient who had drug injection.[7]

In another study, pain ensuing from arterial blood gas sampling was significantly lower in patients who had jet injection of 2 ml of 2% lidocaine compared with those in whom topical lidocaine was applied ($p<0.001$). Pain was evaluated using visual analogue scale score. The number of attempts for successful sampling was considerably higher when using topical lidocaine versus injection ($P=0.009$).[8]

Based on the results of their study, pain of arterial blood gas sampling was decreased significantly in patients who had jet injection of lidocaine prior to the procedure.

Topical lidocaine

The results of a study that compared applying LMX4 (that contains lidocaine 4% and benzylalcohol 1.5%) with hand cream before intra venous cannulation showed 3.2 and 4.67 mean visual analogue scale, respectively. When LMX4 was applied before procedure, pain score was statistically lower ($t=-3.17$, $P=0.003$). Attempts for cannulation did not differ statistically in these two groups.[9] Another study that evaluated venepuncture pain in children 15 minutes after topical 4% lidocaine application reported no statistically significant difference between placebo group and those who were treated with lidocaine [Confidence interval (CI) 95%]. Anxiety did not also differ noticeably (95% CI; $P=0.71$).[10]

Using lidocaine cream before cannulation reduced pain in a study but did not statistically vary pain score in the other study that was conducted on children.[9,10]

Discussion

Lidocaine has various forms of administration, including intravenous, subcutaneous, and nerve blocking. The use of an intravenous lidocaine for its antinociceptive effect was first reported in cancer patients and after surgery, and its analgesic mechanism is known as the blocking of voltage-dependent sodium channels.[11] Lidocaine is effective against both visceral and central pain, and it has less side effects compared with opiates, so it is a better choice compared with opiates.[12] It is a relatively safe drug and does not have significant side effects in low doses. Sensitivity to lidocaine is a hazardous but rare complication. The most commonly reported complications include peri-orbital numbness, vertigo, dizziness, and dysarthria as a result of the accumulation of lidocaine in the body.[11,12] Less frequent complications include tachycardia, allergic reactions, xerostomia, insomnia, tremor, and metallic taste in the mouth. Propitiously, it is an inexpensive and readily available medication and has less side effects than opioids and other analgesics.[13,14] Intravenous route of administration of medications has normally predictable side effects and is safer. As its half-life is short, toxicity symptoms are temporary and they are reversed rapidly; this is one of the reasons why emergency physicians tend to use lidocaine.[12] Commonly, it is used in the treatment of various types of pain, including renal colic, headache, visceral/central pain, neuropathic pain, postoperative pain, post herpetic neuralgia, infiltrative malignant and neurological lesions.[1,12] In a study comparing the use of local lidocaine to the trigger point (1% lidocaine of 10–15

ml) with combined intravenous analgesics (butyl scopolamine bromide of 40 mg + sulpyrine 500 mg + 5% glucose20 mL) for management of renal colic, local lidocaine was considerably superior to the combination of intravenous butyl scopolamine and sulpyrine. Patients in the lidocaine group had significantly experienced less pain. The success rate was 29/30 in the lidocaine group versus 22/30 in the butyl scopolamine group (only one case in the lidocaine group needed added analgesic). No complications were reported in the lidocaine group. Thus, trigger point injection of lidocaine for renal colic is a safe, easy and efficient method.[15]

Topical lidocaine was effective according to a systematic review evaluating its effectiveness in chronic pain management in 2015.[16] Additively, lidocaine patch was found to be effective for subacute and chronic low back pain, post herpetic neuralgia and other neuropathic pain syndromes.[17-19] However, topical lidocaine was not effective for decreasing pain of perineal region after vaginal delivery.[20] Although lidocaine prior to cannulation did not alter success rate in our study, it was shown to increase the visibility of veins and success rate in another study using lidocaine containing creams.[21] In the comparison of procaine and lidocaine for spinal anaesthesia, motor block of lidocaine was higher than procaine at 5 and 10 minutes. Patients who received lidocaine had less sensory block at 5 minutes, but the level of sensory block did not differ substantially at 10 and 20 minutes.[22] Both lidocaine 1% and bupivacaine 0.25% administration for wound suturing alleviated the pain, but patients who had been anesthetized by bupivacaine did not have pain even 5 hours after the procedure while pain returned to roughly pre anesthetic levels after 2 hours in those receiving lidocaine.[23] A study which compared tetracaine hydrochloride 0.5% and lidocaine 2% for pain relief after cataract extraction concluded that patients had similar pain relief.[24] Moreover, lidocaine 60% was more effective than benzocaine20% when used topically prior to dental procedures.[25] It was also shown to be as effective as benzocaine when used as gastro intestinal cocktail.[26]

In addition, it was compared with prilocaine and mepivocaine for nerve block; the success and failure rates of anaesthesia were equal for these medications, and the onset time did not vary substantially.[27]

Conclusion

To draw a conclusion, the efficacy of topical lidocaine is controversial whereas infiltration of lidocaine reduces pain of different procedures in the emergency department.

Acknowledgments

The authors are grateful for participation of health staff who participated in the study, in addition to the staff of the RDCC, Tabriz University of Medical Sciences, Iran. This article is based on a dataset forming part of Roya Najafizadeh's M.D thesis, entitled "Use of Lidocaine for pain management in the Emergency medicine: A systematic review and meta-analysis". It was registered at Tabriz University of Medical Sciences (No: 57916) in 2016.

Conflict of interests

The authors claim that there is no conflict of interest.

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