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The Effectiveness of Intravenous lidocaine in Burn Pain Relief: A Randomized Double-Blind Controlled Trial

Mohammad Haghighi[1], Bahram Naderi Nabi[1], Hossein Khoshrang[1], Siamak Rimaz[1], Soudabeh Haddadi[1], Arman Parvizi[1], Mohammadreza Mobayen[2], Gelareh Biazar[1*], Tayebeh Zarei[3]

Abstract

Objectives: Poor pain control in burn patients as a great public health problem disrupts the healing and rehabilitation process and results in several adverse outcomes. The aim of this study was to investigate the efficacy and safety of intravenous lidocaine in reducing the pain of burn injuries.

Materials and Methods: From August 2014 to March 2015, 66 eligible burn patients participated in the study and were randomly divided into two groups of lidocaine (L) and placebo (P). In group L, lidocaine 2% was injected at a bolus dose of 1.5 mg/kg followed by infusion at the dosage of 1.5 mg/kg/h, and in group P, saline was administrated. Pain severity was measured during 24 hours at baseline and 1, 2, 4, 8, 12, 16, 20, 24 hours after intervention based on Numerical Rating Scale (NRS-11). Morphine consumption, Ramsay score, and side effects were also documented.

Results: Finally the data from 60 patients were analyzed. Comparing baseline with 24 hours after intervention, NRS-11 scores decreased from 7.12±1.42 to 3.33±0.76 ($P<0.001$) in group P and from 6.45±1.02 to 2.50±0.72 ($P<0.001$) in group L. Moreover, the mean of NRS scores during 24 hours in the lidocaine group was significantly lower compared to the placebo group, 3.93±0.72 vs 4.73 ±1.14, ($P=0.03$). The mean amounts of morphine consumption in group L were significantly lower compared to group P, 14.41 ± 4.86 vs 21.07±6.86, ($P=0.001$). The mean of Ramsay score in group L was significantly lower compared to group P, 1.38±0.59 vs 1.45±0.6, ($P=0.014$).

Conclusions: This study revealed that intravenous lidocaine was an effective and safe drug for pain reduction in burn patients.

Keywords: Burn patient, Intravenous lidocaine, Pain relief

Introduction

Burn injuries management is crucial and challenging condition comparing with other wounds (1). In burn injuries, the skin as the first protective barrier has been destroyed and the patient is prone to severe and fetal microbial infections. In order to perfect wound care, regular dressing changes and debridement are vital. However, these repetitive stimuli would be so painful and displeasing and result in long-lasting pain. Therefore the first step should be proper pain control in these patients (2). Burn pain has been described as the worst pain by patients, intense and persistent (3). Studies have shown that uncontrolled pain and anxiety in burn patients result in prolonged healing process and rehabilitation, peripheral and central sensitization, chronic pain, allodynia, hyperalgesia, post-traumatic stress disorder, and depression (4-6). Although firstly pain severity is related to the depth and size of the injury and the severity of inflammatory cascade, later on in the treatment process the quality of pain control and rehabilitation methods, superimposing infection and psychosocial status would be considered as additional important influencing factors (7). Till now several pharmacological and non-pharmacological options have been used for this purpose but still, pain control in burn injuries remains a great concern and a public health problem (5, 8).

Opioid-based analgesia has been used effectively in these patients. However, opioids induce several adverse effects such as opioid-tolerant patients, and opioid-induced hyperalgesia, depressed consciousness, constipation, respiratory depression, hypotension, and delirium (9, 10)

Therefore in order to pain reduction in a safe manner and reduction of the dosage of opioids, other modalities should be investigated (11). In this regard, intravenous lidocaine has been used as a safe and effective option in a limited number of researches (12, 13). The pharmacokinetics and pharmacodynamics of lidocaine have been well known and its properties to treat arrhythmias as well. Additionally, underlying mechanisms for lidocaine infusion properties to alleviate pain has also been described; interaction with sodium channels, reduction of thromboxane A2 and production antagonistic effects on peripheral receptors

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[1]Anesthesiology Research Center, Department of Anesthesiology, Alzahra Hospital, Guilan University of Medical Sciences , Rasht, Iran. [2]Burn and Regenerative Medicine Research Center, Guilan University of Medical Sciences, Rasht, Iran. [3]Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Hormozgan, Iran.
*Corresponding Author: Gelareh Biazar, Tel: +989111350987, Email: gelarehbiazar1386@gmail.com

Key Messages

- Intravenous lidocaine 2% at a bolus dose of 1.5 mg/kg followed by infusion at the dosage of 1.5 mg/kg/h, could be a reliefs to the burn pain.

(14).Studies have shown that lidocaine is a promising safe, novel option in treating of several painful conditions including chronic pain, neuropathic pain, and cancer pain, acting through peripheral and central pain pathways (15-20).

Objectives

The purpose of this clinical trial was to examine the effectiveness of intravenous lidocaine on pain relief in burn-injured patients.

Materials and Methods

This prospective randomized trial was conducted at Velayat hospital, an academic center affiliated to Guilan University of Medical Sciences (GUMS) from August 2014 to March 2015. After the approval of Research Ethics Committee of the University, it was registered in the Iranian Registry of Clinical Trial (IRCT) (Identifier: IRCT201406116186N5; https://www.irct.ir). Furthermore, the study protocol was clearly explained to the patients, and informed consent was taken.

Inclusion Criteria

Age between 18-60 years, American society Anesthesiologists (ASA) I, II, total body surface area (TBSA) burns 20% or greater and second and third-degree burn in upper and lower limbs and trunk.

Exclusion Criteria

Sensitivity to the local anesthetics and opiates, pregnancy, a history of neuropathic and chronic pain, addiction, hepato-renal diseases, cardiac disease, and arrhythmia.

Sample Size

Considering a margin of error $\alpha = 0.05$, $\beta = 010\%$, and an expected power of 90% the appropriate sample size for this survey was 30 cases in each group. Considering the probability of a 10% drop we decided to enroll 66 cases.

Randomization and Blinding

Based on randomized fixed quadripartite blocks our cases were allocated to either the Lidocaine group (L) or Placebo group (P) with the same chance. The study drug and normal saline were prepared and coded by a nurse who was not involved in the study process. In this double-blind study, both the patient and the investigator who assessed the patients and filled out the questionnaire were not aware from the study groups, while the responsible anesthesiologist was aware from the group allocation to any intervention if required.

Intervention

The standard routine monitoring including pulse oximetry (SaO2), ECG, noninvasive blood pressure was performed for all patients after admission to the emergency department. Then pethidine 1 mg/kg/IV was injected and N2O and oxygen were given to the patients using a face mask and the burned area was washed, sterilized, dressed and patients were transferred to the emergency operation room. In group L, lidocaine 2% was injected at a bolus dose of 1.5 mg/kg and then the infusion was continued at a dose of 1.5 mg/kg/h in group P saline 0.9%, was administrated. The patients' pain severity was evaluated at baseline and after1, 2, 4, 8, 12, 16, 20, 24 hours according to the 11-point Numerical Rating Scale (NRS) which is a valid measurement tool for pain intensity in a person who is able to self-report. No pain, scored as 0 and score 10 for the most severe pain that someone can experience. In addition, patients' sedation level was evaluated at the mentioned point times based on Ramsay score at six different levels: 1. Patient anxious, agitated or restless, 2. The patient is cooperative, oriented, and tranquil, 3. Patient responds to commands only, 4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus and 6. Patient exhibits no response (21).

Vital signs including non-invasive blood pressure, respiratory rate and heart rate were monitored for 24 hours. If the patient requested, pain relief medication consisting of intravenous morphine 0.05 mg/kg was administrated and it was also recorded. Additionally any complications such as convulsion, nausea, vomiting, pruritus, urine retention, drowsiness, and respiratory depression were documented by an involved investigator who was blinded to the studied groups.

Statistical Analysis

Data were analyzed by using SPSS version 16. Categorical data are shown as numbers (%), and continuous data as mean ± SD. Chi-square test was used to compare the categorical variables between two groups. To describe the normality of the variables, Kolmogorov–Smirnov test followed by parametric tests were used. In this study repeated measurement test was performed to compare the mean NRS and Ramsay scores at 9 measurement point times. Moreover, a repeated measurement test was applied to assess the effect of interaction between time and groups. A P value less than 0.05 was considered as significant.

Results

From 66 eligible cases who participated in the research, three patients in each group lost the survey. Two patients in group P and one in group L were excluded due to severe pain resistance to morphine and the need for

other analgesics. Additionally, 3 patients were excluded because they were transferred to the intensive care unit (Figure 1). Finally data from 60 patients were analyzed. The difference between the two groups in terms of the demographic data was not statistically significant (Table 1). The mean of blood pressure in group L (78.37 ± 6.82) was significantly lower compared to that in group P (83.59 ±6.41) ($P<0.001$) and the mean of respiratory rate in group L (13.32 ± 0.9) was significantly lower compared to that in group P (14.21 ± 1.08) ($P<0.001$). However, the difference between the two groups regarding the mean of heart rate was not significant (90.14 ± 6.84 vs 89.37 ± 6.41) ($P=0.16$; Table 1).

Comparing baseline with 24 hours after intervention, NRS-11 scores decreased from 7.12 ± 1.42 to 3.33 ± 0.76 ($P<0.001$) in group P and from 6.45 ± 1.02 to 2.50 ± 0.72 ($P<0.001$) in group L. Moreover, the mean of NRS scores during 24 hours in the lidocaine group was significantly lower than the placebo group (3.93 ± 0.72 vs 4.73 ±1.14; $P=0.03$). The mean amount of consumed morphine in group L was significantly lower compared to group P (14.41 ± 4.86 vs 21.07 ± 6.86; $P=0.001$). The mean of Ramsay score in group L was significantly lower compared to group P (1.38 ± 0.59 vs 1.45 ± 0.6; $P=0.014$) (Table 2).

The most frequent side effect was nausea that occurred in 75% of patients in group L and 83.3% in group P. Moreover, convulsion and urine retention occurred in 4.2% in group P. In group L the convulsion was not seen but urine retention occurred in 16 % of patients, the difference between the two groups regarding the mentioned side effects was not significant ($P>0.05$). However, the frequency of vomiting (41.7% vs 8.3%; $P=0.008$) and pruritus (29.2% vs 0%; $P=0.009$) were significantly higher in group P compared to group L.

Discussion

Despite the significant progressions in the pain management of burn patients, dealing with burn wounds pain still remains a tricky challenge (22-24). This mismanagement might be due to the nature of pain presented by patients, inappropriate analgesic administration, and unskilled staff (23,25-30). In this controlled trial; we investigated the effects of lidocaine on pain severity in burn patients. This study revealed that 1.5 mg/kg bolus dose and 1.5 mg/kg/h continuous infusion of lidocaine significantly decreased the pain score and the amount of morphine consumption with lower degrees of sedation based on Ramsay sedation scale. Both NRS and Ramsay scores were significantly lower in group L with no adverse impact on hemodynamic parameters. It was noticeable the frequency of side effects was also lower in group L. In a randomized clinical trial in 2011, Wasiak et al (31) evaluated the effects of adding lidocaine to morphine in 45 burn patients. They measured the pain intensity, time to rescue analgesia, the amount of opioids consumption, patient satisfaction, and the degree of anxiety. In line with

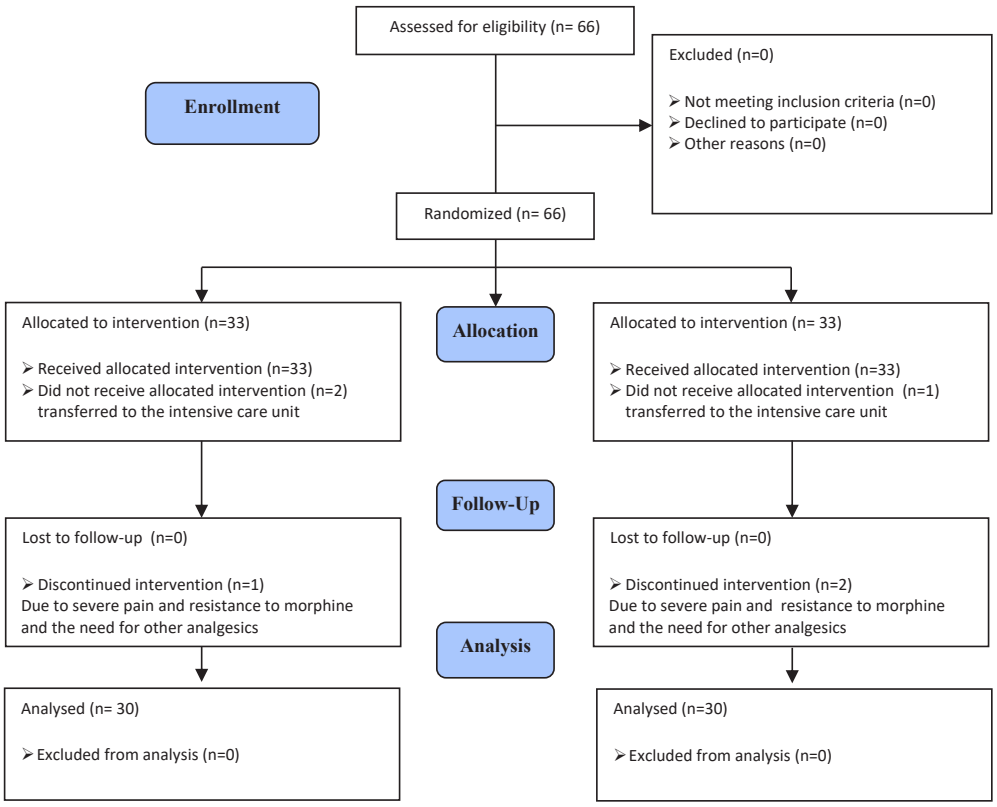

Figure 1. The Study CONSORT Flowchart.

Table 1. Demographic and Hemodynamic Characteristics of Patients in Two Groups

Variables	Groups		*P* Value
	Lidocaine	Placebo	
Gender (male), No. (%)	18 (62.5)	22 (73.33)	0.2
Gender (female), No. (%)	12 (37.5)	8 (26.66)	
Age (y)	39.58±10.17	34.16±13.07	0.11
ASA class I/ II	23/7	24/6	0.966
Burning, TBSA	28.00±6.97	26.08±6.15	0.31
Mean blood pressure (mm Hg)	78.37±6.82	83.59±6.41	<0.001
Respiratory rate (breaths per minute)	13.32±0.9	14.21±1.08	0.001
Heart rate (beats per minute)	90.14±6.84	89.37±5.62	0.16

Abbreviations: ASA class, American Society of Anesthesiologists physical status classification system; TBSA, Total body surface area.

Table 2. The Comparison of the Mean of NRS-11, Morphine Consumption and Ramsay Score of Patients Between the Two Groups

Variables	Groups		*P* Value
	Lidocaine	Placebo	
NRS (h)			
0	6.45±1.02	7.12±1.42	*P*=0.03 F=2.62
1	4.54±0.50	5.5±1.71	
2	4.41±0.88	5.79±1.58	
4	3.95±0.62	4.41±1.69	
8	4.04±0.95	5.25±0.73	
12	3.62±0.64	4.08±1.21	
16	3.04±0.55	3.83±1.23	
20	2.83±0.63	3.33±0.76	
24	2.50±0.72	3.33±0.76	
	F=77.5, *P* < 0.001	F=69.8, *P* < 0.001	
Amount of consumed morphine (mg)	14.41±4.86	21.7±6.86	<0.001
Ramsay score	1.38±0.59	1.45±0.6	0.014

Abbreviations: NRS, numerical rating scale.

our findings, they indicated that lidocaine significantly decreased NRS scores, however in opposite to this work, no significant difference regarding the amount of opioids consumption was observed (32).

In this study the frequency of vomiting and pruritus in the lidocaine group was significantly lower than which was observed in placebo group, however, as mentioned above Wasiak et al (31) did not report any significant difference regarding side effects such as pruritus and vomiting. This discrepancy may be due to the lack of difference in morphine consumption between case and control groups in Wasiak et al (31) trial, so morphine equally was given to case and control groups and resulted in similar side effects in two groups. The other possible justification could be that, pain killer supplies vary due to the different painful procedures that the patient receives, so, this makes differences in the amount of administrated analgesics to the patients in different studies (33-36). Furthermore studied populations are not the same in terms of their perception towards the definition of pain severity and NRS is an objective scale. In line with this study, Wu et al demonstrated that lidocaine could significantly alleviate thermal pain during healing process. They supposed that changes of miRNAs expression profile was the underlying mechanism (32). Abdelrahman et al in a prospective double-blind controlled trial demonstrated that continuous infusion of lidocaine 180 mg/h could significantly reduce the pain in burn patients and opioid consumption(13). Supporting our findings another study conducted by Jönsson et al evaluated the effects of intravenous lidocaine infusion on pain reduction in patients with second-degree burns, three days after injury and indicated that lidocaine, significantly decreased the pain severity without additional opiate requirement (37). Cassuto and Tarnow in a case report presented an 18 years old patient with 20% burn injuries that administration of 5 mg morphine on admission and 9 mg during the first seven hours did not control the severe pain but a bolus dose of lidocaine 75 mg followed by 3.4 mg/kg/h continuous infusion, successfully controlled the pain (38).

Although intravenous lidocaine has been a well-known agent in patients with arrhythmia and neuropathic pain (39), regarding burn pain, the shreds of evidence are not sufficient (37,38). Indeed, to find the optimal dosage and timing of the drug administration and to establish these results and better understanding that whether lidocaine is a true pain modifier in patients with burn injuries, further well-designed controlled clinical trials with longer follow-up duration and larger sample size are required.

Limitation

The trial was conducted at a single center, and it had a small sample size. Additionally, only patients in ASA class I and II were included.

Conclusions

This study revealed that intravenous lidocaine was a safe and effective treatment option for pain reduction in burn patients with at least side effects. Of course, further well-planned trials are welcomed to confirm these findings.

Authors' Contribution

Conceptualization: Bahram Naderi Nabi.
Investigation: Mohammad Haghighi, Gelareh Biazar.
Resources: Mohammadreza Mobayen, Hossein Khoshrang.
Data Curation: Mohammad Haghighi, Arman Parvizi.
Writing–original draft: Tayebeh Zarei, Gelareh Biazar.
Writing–review and editing: Siamak Rimaz, Soudabeh Haddadi.
Supervision: Bahram Naderi Nabi.

Conflict of Interests

None.

Ethical Issues

Ethical approval for the study was obtained from the ethics committee of Guilan University of Medical Sciences (No. IR.GUMS.

REC.1920422812). The aim and method of the study were explained to the patients, and informed written consent was obtained.

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