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Systematic Review

Intravenous Lidocaine in Management of Acute Pain in Traumatic Limb: Evidence-Based Systematic Review

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ABSTRACT

Lidocaine is one of the medications that is proposed as an alternative in acute pain management. Lidocaine is routinely used in topical and dental anesthesia and is known for its analgesic effects. But various evidences are proposing an intravenous administration of lidocaine for pain management; while in acute limb pain, its safety, and efficacy are not reviewed yet. In this review study, PubMed, Medline, Scopus, and EMBASE were quarried for studies on an acute traumatic limb injury pain treated with intravenous lidocaine. Critical Appraisal Skills Program and GRADEpro tools were used to critically evaluate the collected literature based on the evidence-based approach. Recommendations were synthesized based on the highest levels of evidence. Eleven studies were included in the review. While some studies were showing effective analgesic properties of intravenous lidocaine for pain relief in extremities when compared with conventional opioids, the high rate of Adverse Events (AEs) reported in some studies and the need for a close observation of patients for major side effects restrict clinical application of the systemic lidocaine. Blood lidocaine level studies are required but are missing in the literature. Post-operative outcomes of limb trauma patients who receive lidocaine are not clear. The AEs' monitoring is not followed during the hospitalization or after discharge. Systematic review and meta-analyses on the topic are heterogeneous due to different indications of intravenous lidocaine administration. Our systematic review of literature could draw the conclusion of cautions on high dose intravenous lidocaine administration due to potential side effects and unclear outcomes.

GRAPHICAL ABSTRACT

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Introduction

Any injury or damage caused by physical or chemical agents to body tissues is called trauma [1, 2]. Today, trauma is one of the most important causes of death and disability in the world [2]. The initial treatment measures in acute traumatic events of limbs, fractures, and lacerations include bleeding control, shock prevention, and applying the method of immobilizing the damaged limb, which also reduces the intensity of pain [3]. Despite the remarkable progress that has been made in the field of acute postoperative pain control, unfortunately during the last two decades, the prevalence of acute pain in setting of the emergency department has not decreased [4, 5]. Although injuries to the musculoskeletal system are very common in various traumas, they rarely cause potentially dangerous injuries [6]. These types of injuries are dangerous when they cause severe external or internal bleeding. Mild to severe traumas can cause damage to the musculoskeletal system of the body [7]. Depending on the type and severity of the trauma, different types of injuries occur in the upper and lower limbs. These injuries may occur from mild (superficial) to severe injuries. Pain management in acute limb traumatic injury has different medical choices available [8]. The conventional application of the opioids is accepted to relief pain in most patients [9]. While in some circumstances like opioids dependance or severe injuries, pain might not get relieved by multiple opioids that necessitate alternative treatments [10]. Lidocaine is one of the medications that is proposed as an alternative. Lidocaine is being routinely used in topical and dental anesthesia and is known for its analgesic effects [11, 12]. However, various evidences are proposing intravenous administration of lidocaine for pain management [13-15]; while in acute limb pain, its safety and efficacy is not reviewed yet. To permanently improve patient care, the World Health Organization (WHO) has emphasized that health care should be based on the best scientific evidence. Today, the main basis of diagnosis and treatment in medicine is the evidence obtained from research, and one of the movements that have tried to achieve this basis is evidence-based medicine. Today, the main basis for diagnosis and treatment in medicine is the evidence obtained from research. One of the movements that have tried to achieve this basis is Evidence-Based Medicine (EBM). In this study, we would systematically review the current evidences of the intravenous administration of lidocaine for pain management of acute traumatic limb injury in the ED settings.

Materials and Methods

This was a systematic review based on the PRISMA protocols. For studying question design, the PICO approach (Population, intervention, comparison, and outcome) was carried out. Based on the PICO model, study questions were synthesized.

The research population was patients experiencing acute pain following the limb trauma. As we are reviewing the chain of pre-hospital and Emergency Department, Traumatic limb pain needed to be evaluated on the day of the trauma event by a single incident. Traumatic limb injury had to be incident of a penetrating, blunt, and deceleration mechanism of trauma with no further trauma in other parts of the body [16]. Heat, freezing, and electrical injury were not included to concentrate study filed on isolated limb injuries. Intervention was any pain management approach based on the lidocaine administration. Comparisons were made for the efficacy of intervention in pain management; while instead of considering pain-free state as the **o**utcome, we considered limb health as the outcome to address the major and minor adverse events in our review. Major adverse events in limb were extracted from Common Terminology Criteria for Adverse Events v3.0 (CTCAE) [17] to address the possible effects of the analgesia in masking the physical examination [18], and also bone fracture, or ulcer healing process, as shown in the following Figure 1.

Exostosis	Undiagnosed Fracture
Acute compartment syndrome	Hypoplasia
Gait disorder	Myositis
Fibrosis-deep connective tissue	Soft tissue necrosis
Osteonecrosis	Joint-effusion

Figure 1. Potential adverse events associated with undiagnosed orthopedic trauma

Eligibility criteria

The inclusion criteria were studies evaluating the effect of intravenous lidocaine for pain management in acute limb pain due to physical trauma in adults. Studies on chemical or electrical injuries were not retrieved. Studies on critically ill traumatic patients were also not included. Studies in operating room setting were not considered. Studies had to be in English or Persian language.

Evidence collection

PubMed, Medline, Scopus, and EMBASE databases were queried for data collection. The search strategy was developed based on a primary literature review and study questions. MeSH terms were used to search the databases. The search strategy is displayed in Table 1. The search strategy was running by two independent researchers. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in collecting evidence. One search was carried out to find relevant evidence on administration of lidocaine in acute pain situation and one for the potential adverse events of the lidocaine administration on limb health.

Table 1. Search strategy of SR in PubMed, Medline, Scopus, and EMBASE databases

PubMed	
1. ("pain" OR "Orthopedic pain" OR "Acute fracture pain" OR " Acute fracture " OR " Limb fracture " OR "limb trauma" OR " Traumatic injury" OR "Acute Musculoskeletal Injury" OR "limb trauma") AND ("Lidocaine" OR "intravenous lidocaine" OR "lidocaine" [title]) AND "Analgesia" AND "Morphine" NOT ("postoperative" [Title] OR "dental" OR "phantom")	
2. ("acute compartment syndrome" OR “necrosis” OR “myositis” OR “Osteonecrosis” OR “Hypoplasia” OR "undiagnosed fracture") AND ("Lidocaine" OR "intravenous lidocaine" OR "lidocaine" [title])	
Medline, Scopus and EMBASE	
1. Pain/	11. Limb trauma/
2. Orthopedic pain	12. Lidocaine/
3. Acute fracture pain	13. Intravenous lidocaine
4. Acute fracture/	14. Analgesia
5. Limb fracture	15. Morphine
6. Limb trauma/	16. 1-9 or. mp
7. Traumatic injury	17. 10-11 or. mp
8.Acute Musculoskeletal Injury	18. 12-13 or.mp
9. Acute Musculoskeletal Injury	19. 14 and 15 and 16
10. Acute Musculoskeletal Injury	

In the final review, a total of 378 articles were obtained in the initial search and removal of the duplicated records, 54 articles that seemed relevant based on the abstract and title were used for full text review. Relevant studies were quarried in hand-search of reference list of full text evaluated articles. A checklist containing study ID, year of publication, country, setting, design, sample size, Age of participants, patient characteristics, lidocaine route of administration, comparison, outcome, adverse outcomes, and prognostic factors was completed for each record.

Risk of bias and synthesis of evidence

After obtaining the full text, the articles were initially reviewed in terms of title, and then in terms of their abstracts, and related articles obtained after this stage were subjected to a Critical Appraisal Skills Program (CASP) by the proper tool. After critical review of articles according to CASP tool, systematic review articles with a score of 7 and more (out of a total score of 10, randomized clinical trial articles with a score of 8 and more (out of a total score of 11), and cohort and cross-sectional studies with a score of 7 or higher (out of a total score of 11) were selected for the final review. The grading of recommendation, assessment, development, and evaluation (GRADE) method was used to synthesis the evidence, based on the online program of the GRADEpro [19]. Levels of evidence were ascertained to articles based on the hierarchy of evidence [20].

Results and Discussion

Finally, 11 studies were included in review. There were 4 SR studies with a low level of evidence for our hypothesized objective and 5 RCTs with a high quality. There were also two case report studies at the lowest level of evidence. Two SR studies were conducted on studies performed in the ED setting. MA was carried out in two studies (Table 2). E Silva *et al.* SR contained only one study on critical limb ischemia (Vahidi *et al.*) [21] that we already had included in our own review to evaluate dependently. Buck *et al.* developed a guideline on the Lidocaine administration for pain management. Their pain of interest was not similar to our study aim, but they provided important recommendations. They stated that a test dose of lidocaine might be suggested for 60 minutes (based on low quality evidence); they summarized contradictions of intravenous lidocaine to conduction block, bi-fascicular block, allergy, pregnancy, infancy, ECG widening of QRS complex, or increased PR interval, use of Antiarrhythmic medications, hepatic disease, and alcoholism [22].

Zhong *et al.* included 2 studies on musculoskeletal originated pain. Their MA with low heterogeneity levels showed statistically lower pain in lidocaine groups than controls in 15 minutes and 30 minutes, but not 60 minutes [23].

Zhu *et al.* [24] stated short term analgesia without a long standing effect of lidocaine for diverse etiologies of pain; while high dose of 5 mg/kg being used in most of their reviewed studies.

In RCTs, Attal *et al.* showed that lidocaine was better than placebo and they showed that the etiology of pain (post herpetic neuropathic or traumatic) was not predictive of the response [25].

Farahmand *et al.* found no significant difference of interventions. However, Forouzan *et al.* and Vahidi *et al.* showed that lidocaine was better than Morphine in analgesia of acute limb pain. None of studies had reported longer outcomes. Case reports were reporting successful pain management in patients with acute limb pain in a low level of evidence.

Based on the appraisal, evidences collected for this study are ranging from I to IV. Risk of bias and impact on the evidence synthesis is indicated in Figure 2. The SR studies had evaluated pain in ED or other settings, without considering the etiology and physiology of pain; the pooled evidence was synthesized that was a source of bias in some studies.

Based on the GRADE scale, judgments were summarized in Figure 3. This figure displays the priority of this problem for the health sector and considers cost benefits along with summarizing main effects of the intervention.

Table 2: Characteristics of included studies

	SR	SR	536		pain in ED	intravenous	diverse	NRS	20/225	NA
e Silva et	SR	Guideline	-		painful	intravenous	diverse	diverse	diverse	NA

al. [21]					patients in all settings					
Zhong et al. [23]	SR-MA	SR-MA	1351		pain in ED	intravenous	NSAIDs	mean pain	no significant difference in the rate of AEs compared to controls	NA
Zhu et al. [24]	SR-MA	SR-MA	250		neuropathic pain	intravenous	placebo	mean pain	132/250 vs. 53/250	NA
RCTs										
Attal et al. [25]	outpatient pain center	double blind controlled RCT	22	50.9	traumatic nerve injury (14) and postherpetic neuralgia (8) at beginning	5mg/kg intravenous over a 30-minute	placebo	VAS till 6 hours and allodynia relief	72% side effect with 5 mg/kg IV during 30	NA
Farahmand et al. [26]	single center	double blind controlled RCT	50	31.4	extremity trauma	1.5 mg/kg intravenous over 2-3 minutes	intravenous morphine	60 min pain severity	no AEs reported	NA
Forouzan et al. [27]	single center	double blind controlled RCT	280	31.47	Extremity Fractures	1.5 mg/kg intravenous over 2 minutes	intravenous morphine	VAS till 30 min	no AEs reported	NA
Foroughian et al. [in persian] [29]	single center	double blind controlled RCT	60	35.31	extremity trauma	1.5 mg/kg intravenous slowly (over 2 to 3 minutes)	intravenous morphine	VAS till 60 min	2 AEs were reported versus 5 in morphine	NA
Sin et al. [31]	case study	case report	1	17	ankle injury	intravenous lidocaine	-	Patient did not respond to morphine and IV lidocaine was administered.	-	NA

	LOE	Certainty assessment					Impact		Importance
		N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision		
e Silva et al.	I	8	randomized trials	serious a	not serious	not serious	serious b	*	IMPORTANT
Buck et al.	I	NA	Diverse designs	very serious, c	not serious	not serious	not serious	indications and contraindications of lidocaine administration were discussed.	CRITICAL
Zhong et al.	I	12	RCT	serious a	not serious	not serious	not serious		CRITICAL
Zhu et al.	I	26	RCT	serious a	not serious	not serious	not serious	high rate of AEs	CRITICAL
RCTs		Randomization process	Deviation from intended interventio n	Missing outcome data	Measurement of outcomes	Selection of reported result	Overall risk of bias		-
Attal	II	Low risk	Low risk	Low risk	Low risk	Low risk	High risk, a		-
Farahmand et al.	II	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk		-
Forouzan et al.	II	Low risk	Low risk	Low risk	Low risk	High risk	High risk		-
Vahidi et al.	II	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk		-
Foroughian et al. [in persian] (29)	II	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk		-
Case reports									
Gharaei et al.	VI	-	-	-	-	-	-	-	-
Sin et al.	VI	-	-	-	-	-	-	-	-

Figure 2: Grade evidence table for individual studies with RCT quality appraisal (a: inadequately defined patient characteristics (selection bias); b: Drawing conclusions based on diverse and small sample size evidence; c. No proper SR design; * Lidocaine effect was observed for 6 RCTs on different diseases of migraine, renal colic, acute limb ischemia, etc in comparison to various other interventions; while giving good statistics on adverse events rate (8.9%; 95% CI of 5.5 to 13.4%); LOE: Level of evidence)

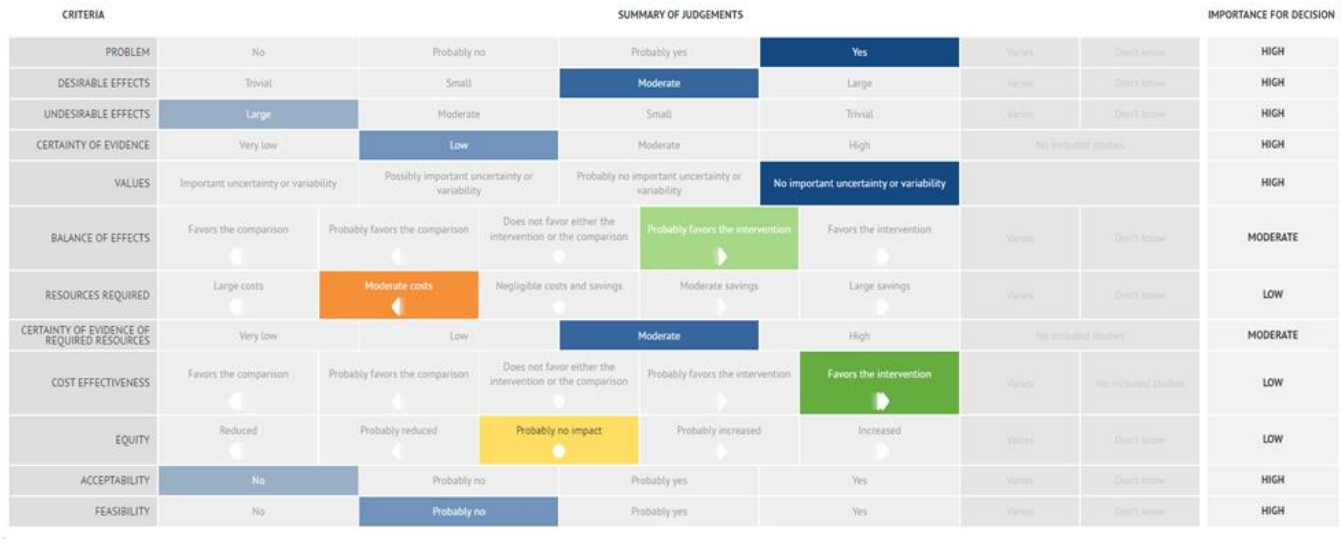

Figure 3: Screenshot of GRADE scale for the evidence summary

Our study summarized the recent pieces of evidence on lidocaine administration for acute traumatic limb pain. The evidence quality was totally low to draw a conclusion and much further research is needed. However due to some extent of reported adverse events in the literature, there are cautions in clinical practice for the administration of IV lidocaine. Evidence

reveals the possibility of lidocaine toxicity even with the topical forms [30]. Lidocaine toxicity might not occur at doses lower than 4.5 mg/kg [32]. Lidocaine at doses of 75 mg might be administered in spinal anesthesia [33]. In the setting of the acute traumatic extremity injury, this might be missed and the anesthesiologist might not get informed of the previous blouses of lidocaine. This can lead to lidocaine toxicity and increased adverse events. The second point is that there are no longer follow-ups than ED is available. In addition, some minor shreds of evidence show the possibility of compartment syndrome following the intravenous lidocaine injection [34]. In regional intravenous anesthesia, that is also known as the bier block, multiple cases of compartment syndrome have been reported when using lidocaine [35]. But, it is not clear whether this is the consequence of the technique or the lidocaine. On the other hand, an experimental study clearly shows that the technique of bier block itself, when normal saline is injected, is not associated with increased tissue pressure [36]. Hence, the lidocaine effect on the increase of tissue pressure remains potential. Injection of 360 mg in one case, and 200 mg of lidocaine in another case, along with other sedatives was associated with compartment syndrome in Ananthanarayan *et al.* study [34]. A systematic review of case reports (level IV evidence) showed that 1.4 mg/kg and 2.5 mg/kg of lidocaine intravenous injection in tourniquet extremity was associated with seizure and cardiac arrest, respectively [35].

Many studies have been conducted on the risk of nonunion in different extremity fractures based on analgesic medications. High-level evidence has investigated the nonunion risk after NSAIDs or opioids administration in fracture patients [37-39], but such information does not exist for lidocaine.

Our PICO model primary literature review revealed that the problem of traumatic extremity pain in an ED setting is a priority for the clinicians. However, having uncertainty in the pooled evidence and large extent of undesirable effects, even cost-effectiveness issues remain in favor of the conventional practice of the pain management as there might be the need for further monitoring and evaluations before the lidocaine administration. Conventional treatments approved for traumatic injury analgesia include NSAIDs and opioids [40] that could be used in combination and various different routes before trying alternative medications. In case of the opioid's contradictions, as lidocaine has similar hepatic pathways of metabolism, lidocaine may not be further indicated. But, it can be used in safe doses to decrease the need for rescue analgesics.

Foroughian *et al.* [29] find that lidocaine was better in short-term analgesia than morphine (15 min); as well meta-analysis of Zhong was showing same short-term differences till 30 minutes of administration [23]. It seems that lidocaine might be better for acute pain as is showing short-acting analgesics effects in traumatic extremity pain.

Recommendation

We recommend anesthesia consultation prior to intravenous lidocaine administration for dose adjustments for possible upcoming spinal anesthesia for the operation; while not having lidocaine blood level screening tests available would make challenging circumstances for spinal anesthesia. We recommend a proper systematic physical examination and electrocardiogram request prior to intravenous lidocaine administration for evaluation of contraindications. We recommend the maximum dose of the 2 mg/kg over with rescue lidocaine if no AEs happened at 60 minutes.

We recommend intravenous lidocaine administration in patients who are at a low risk for acute compartment syndrome.

We recommend intravenous lidocaine administration for younger subjects based on the current evidence.

Conclusion

While some studies are showing effective analgesic properties of the intravenous lidocaine for pain relief in extremities when compared with the conventional opioids, the AEs' high rate was reported in some studies and the need for close

observation of patients for major side effects, restrict clinical application of the systemic lidocaine. Older age patients should be considered for dose adjustment and more detailed monitoring for AEs due to less tolerance to potential cardiotoxic effects of the lidocaine. Blood lidocaine level studies should be conducted in case of further studies in this era. Post-operative outcomes of limb trauma patients requiring operation should be included in further research. Monitoring of AEs should be followed during the hospitalization.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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