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Review Article

Resistance to Local Anesthetics in Patients with a History of Scorpion Stings: A Systematic Review

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ABSTRACT

Background: Scorpion stings have been reported to induce inadequate block or block failure in local anesthesia. The present study has reviewed the resistance to local anesthetics in patients with a history of scorpion stings.
Methods: Articles from domestic and foreign journals in databases such as SID, IranMedex, Magiran, Uptodate, Google Scholar, Cochrane, Scopus, and Web of Science from 2010-2024 were searched, and ultimately 13 related high-quality articles based on STROBE were included in this review.
Results: According to the results of the included studies, which have dealt with scorpion sting cases and resistance to local anesthetics, patients with a history of scorpion stings experience significantly prolonged times of onsets for both sensory and motor blocks and the peak of sensory and motor blocks. Some of these patients have failed/inadequate sensory and motor block.
Conclusion: According to the mentioned materials, the prevalence of resistance to local anesthetics is higher in patients with a history of scorpion stings.

Introduction

Scorpions are a group of arachnids that are about 450 million years old [1]. There are over 150 types of scorpions worldwide, with only 50 posing a danger to humans [2-3]. Scorpion stings are one of the main problems in tropical and subtropical regions [4]. The clinical severity of a scorpion sting depends on various factors, including the scorpion's genus and species, the number of stings, the volume of venom injected, the season during which the sting occurs, and the physiological condition of the scorpion. Additionally, the age and overall health of the affected individual play a crucial role in determining the clinical outcome [3-5]. A very diverse range of scorpion species reside in Iran, where the dangerous species have already been discovered [6-7]. Approximately 250,000 cases of venomous animal stings are being recorded annually in Iran, with about 50,000 of them being scorpion stings, leading to around 50 deaths per year. However, the actual frequency of stings is estimated to be 2-2.5 times higher [8]. While cases of death due to scorpion stings occur in all regions throughout the country, around 75% of them happen in Khuzestan, Sistan and Baluchistan, Kerman, and Hormozgan provinces.

Local anesthetics function by blocking voltage-gated sodium channels, which disrupts the transmission of nerve signals. These drugs are categorized into two main chemical groups: aminoesters and aminoamides. Existing local anesthetics often lack potency and specificity because their binding site on sodium channels offers

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limited structural constraints. Their properties are influenced by the necessity for high solubility, rapid reversal of protonation, and efficient diffusion through both aqueous and lipid environments within biological membranes. The reversible protonation of tertiary amine groups means that the charge of local anesthetics is pH-dependent; they become less charged in alkaline conditions and more charged in neutral or acidic conditions. Aminoesters are predominantly metabolized by plasma esterases, while aminoamides are primarily broken down by hepatic enzymes linked to the cytochrome P450 system. Systemic toxicities related to local anesthetics mainly affect the heart (e.g., atrioventricular conduction block, arrhythmias, myocardial depression, and cardiac arrest) and the brain (e.g., agitation, lethargy, seizures, and generalized central nervous system depression). These toxicities can be exacerbated by conditions such as hypoxemia and acidosis. Resuscitating a patient from a bupivacaine overdose is particularly challenging, emphasizing the importance of preventing intravascular injection or overdose. For major nerve blockades, incremental and fractionated dosing is recommended to enhance safety. Ultrasound can effectively lower the risk of systemic toxicity, while Intralipid serves as a valuable aid during resuscitation. At concentrations found in commercial formulations, local anesthetics exhibit inherent neurotoxicity. During regional anesthesia, intraneural concentrations are typically (but not always) below the toxic threshold, as the solution spreads through surrounding tissues and diffuses from injection sites into the nerve. However, the risk of localized toxicity increases when injections are made into confined tissue spaces. To ensure the safe and effective use of local anesthetics in regional anesthesia, it is essential to consider the following factors: the patient's specific clinical condition; the desired location, intensity, and duration of regional anesthesia and analgesia; anatomical aspects influencing drug deposition near nerves; and the selection and appropriate dosing of the anesthetic agent. The evaluation of clinical effects following the administration of single-stereoisomer formulations of local anesthetics, rather than racemic mixtures, has aimed to minimize systemic toxicity and enhance sensory selectivity. However, true sensory selectivity remains unattainable with the medications currently available. Promising research directions to improve the efficacy of local anesthetics include developing slow-release formulations, targeting specific sodium channel subtypes, and focusing on nociceptive fibers [9].

Under certain circumstances, spinal anesthesia may fail due to factors such as inadequate distribution relative to the surgical needs, injection failure, technical errors, drug-related issues, pseudo-block failure caused by unrealistic expectations of block onset speed, subdural injection of the spinal dose, or true resistance to local anesthetics (LA) [10]. Although it is rare for systemic anesthesia (SA) failures to result from physiological resistance to local anesthetics, a history of repeated failures with dental or other anesthetic techniques raises the possibility of sodium channel mutations rendering these drugs ineffective [11]. For instance, the A572D mutation in the SCN5A gene encoding Nav1.5 was identified in cases where an entire family exhibited resistance to LAs [12]. Evidence suggests several conditions linked to LA resistance, including mutations in voltage-gated sodium channels (VGSCs) [12], exposure to scorpion venom [13], Ehlers-Danlos syndrome [14], insufficient LA efficacy in regular opioid users [15], and reduced LA effectiveness in individuals with naturally red hair [16]. Reports of LA resistance are often met with skepticism, as the drugs are difficult to detect. However, because LAs theoretically target structural or mutational disorders via sodium channels, varying responses to these drugs can occur. Nine distinct VGSC isoforms are responsible for initiating and propagating action potentials in the mammalian nervous system, with the Nav1.7 isoform playing a critical role in transmitting nociceptive signals [17]. Sodium channels are known to be influenced by scorpion venom, which slows the decay phase of the whole-cell Na+ current in the presence of the toxin [17]. Research supports the voltage-sensor trapping model of alpha-scorpion toxin action, in which the toxin hinders the conformational changes in the domain IV voltage sensor that typically lead to rapid channel inactivation [17].

This study aimed to investigate the prevalence of resistance to local anesthetics in patients with a history of scorpion stings.

Methods

In this systematic review, articles published during 2010-2024 in domestic and international journals available in databases including the Scientific Information Database (SID), Iran Medex, Magiran, Uptodate, Google scholar, Cochrane, Scopus, and Web of Science were searched. The keywords included the Persian words and their English equivalents for: scorpion sting, scorpion bite, local anesthetics, resistance. All cross-sectional studies examining scorpion sting-induced resistance to local anesthetics were incorporated. The articles were searched simultaneously and evaluated for their quality by two researchers separately to increase the validity and reliability of the studies. Initially, a list of titles and abstracts of all the available articles were prepared and examined to determine and select the relevant titles. Then related articles were entered into the research process independent of all cases. At the end of

the search, 10 articles that were of good quality were included in the systematic study.

Results

The included studies are listed in (Table 1). The information regarding the effect of time and number of stings is also summarized in (Table 2). As there has been little research pertaining to the treatment, a definite solution cannot be suggested, and therefore, some of them are briefly mentioned in the discussion session.

Table 1- General findings regarding local anesthetic resistance induced by scorpion sting

	Author	Ref	Year	Design	Sample Size	Findings
1	Minnu Mridul Panditrao	[18]	2012	Case report	1 patient	Exposure to single or multiple scorpion stings may lead to the development of resistance to local anesthetic drugs administered through various routes for achieving nerve blocks.
2	Mridul M Panditrao	[19]	2013	Case–control study	70 patients (n=70) of either sex, in the age range of 18 and 80 years	Patients with a history of scorpion stings displayed apparent resistance to the effects of bupivacaine during spinal block procedures.
3	Mridul M. Panditrao	[20]	2013	Case report	1 patient	Exposure to single or multiple scorpion stings may lead to the development of resistance to the effects of local anesthetic drugs administered through various routes for achieving nerve blocks.
4	Mridul M Panditrao	[13]	2015	Case–control study	70 randomly selected patients	Suggests that prior exposure to single or multiple scorpion stings may result in the development of resistance to local anesthetic agents.
5	Durga Kosam	[10]	2015	Case–control study	40 patients in the age range of 18-80 years	In the scorpion sting group, both the onset time for sensory and motor blocks and the time to reach their peak effects were significantly delayed.
6	Ahmet Issin	[21]	2015	Case report	1 patient	Exposure to single or multiple scorpion stings may contribute to the development of resistance to local anesthetics.
7	Venkata Ramana Murthy V	[22]	2017	Case–control study	patients with age group between 21-58 yrs	Scorpion stings can lead to resistance with an immunological basis, potentially involving a mechanism of competitive antagonism.
8	Gokulakrishnan G	[23]	2019	Case report	1 patient	The onset times for both sensory and motor blocks, as well as the time required to reach their peak effects, are significantly delayed, with some cases even resulting in complete failure.
9	R John Varghese	[24]	2022	Case report	1 patient	Scorpion toxins induce repetitive action potentials and sustained depolarization of sodium channels within nerve axons, disrupting normal nerve signaling and function.
10	Sonali Tripathi	[25]	2023	Case–control study	40 patients	This study found that patients with a history of scorpion stings exhibited a notable failure rate in spinal

						anesthesia, indicating a possible resistance to local anesthetic agents.
11	Gautam A.	[26]	2023	Observational, monocentric, prospective, single blind	33 patients, Bi-gender, Age: 18-70 y	"The duration since a scorpion sting significantly influences the effects of spinal anesthesia on sensory and motor blocks. However, the number of stings does not appear to impact the sensory and motor characteristics of spinal anesthesia.
12	Amrita rath	[27]	2023	Case–control study	2 patients	Spinal anesthesia block (SAB) with 3 ml of 0.75% hyperbaric ropivacaine has been shown to assist patients with a history of scorpion stings in achieving an adequate block.
13	Kajal S Dalal	[28]	2023	Case report	2 patients	Exposure to single or multiple scorpion stings has the potential to cause resistance to the effects of local anesthetics.

Table 2- The effect of time and number of stings on resistance

	Author	Ref	Year	Design	Sample Size	Effect of time and number of stings
1	Mridul M Panditrao	[19]	2013	Case–control study	70 patients (n=70) of either sex, in the age range of 18 and 80 years	It was observed that patients who experienced multiple or recent scorpion stings—within the past 8 months—showed complete failure of the spinal block, requiring a transition to general anesthesia for adequate management.
2	Mridul M Panditrao	[13]	2015	Case–control study	70 randomly selected patients	The greater the number of scorpion stings or the more recent the exposure, the higher the likelihood of block failure. Patients with the highest number of stings (3–4) occurring in the most recent past experienced nearly complete block failure.
3	Durga Kosam	[10]	2015	Case–control study	40 patients in the age range of 18-80 years	Patients exhibit greater resistance when a scorpion sting is more recent, resulting in a significantly prolonged onset time for both motor and sensory blocks.
3	Venkata Ramana Murthy V	[22]	2017	Case–control study	patients with age group between 21-58 yrs	Twelve patients with a history of single or multiple scorpion stings within the past year exhibited complete lack of anesthetic effect. Additionally, six patients who had experienced scorpion stings more than two years ago showed a delayed response to Articaine, with an average onset time of 20 minutes, while remaining unresponsive to Lidocaine and Mepivacaine.
5	Gautam A.	[26]	2023	Observational, monocentric, prospective, single blind	33 patients, Bi-gender, Age: 18-70 y	Patients exhibit greater resistance when a scorpion sting is more recent. Those stung within the past six months experience complete block failure. Additionally, there is no significant difference in resistance between patients with a history of single or multiple stings.

Discussion

Possible Mechanism for Anesthetic Resistance: Competitive antagonism in spinal anesthesia failures can explain the mechanism through which the scorpion toxin acts [29]. Scorpion toxins (ScTxs) that specifically target voltage-gated sodium channels (Na V) fall into two categories: α-ScTxs and ß-ScTxs, which change the voltage-dependent activation to more negative membrane potentials, resulting in firing in nerves and muscles. The ß-scorpion toxin traps the IIS4 voltage sensor in its

activated position as it moves outward in response to depolarization and holds it there, slowing its inward movement upon deactivation and enhancing subsequent channel activation [30]. Most of our study results can also be attributed to the antagonism at the binding site [11, 13, 31-34]; however, more research has to be conducted to find out the exact cause of anesthetic failure.

To what extent will patients with a history of scorpion stings experience local anesthetic resistance? Patients with scorpion stings experience significantly prolonged onsets and peak times for both sensory and motor blocks, while some of them have failed or reached inadequate sensory and motor blocks [27]. Furthermore, patients with a history of scorpion stings have shown no resistance to Ropivacaine. Further studies are needed to prove these issues [18]. (Table 2) contains information regarding how time and number of stings are effective in resistance. According to Gautam A. et al. [26], the duration between a scorpion sting and an attempt at local anesthesia plays an important role in the intensity of resistance to SA: less than six months will lead to a complete SA failure, but the resistance starts to lessen after a year [26]. No significant differences have been observed between patients with single and multiple scorpion stings. However, one study indicates that individuals with multiple stings tend to experience a delayed onset of motor block [19].

The common solution to this type of resistance would be to either use general anesthesia or opioids in SA; however, some case reports suggest the use of Ropivacaine or Meperidine through spinal anesthesia [27, 35]. A case-control study focusing on patients with a history of scorpion stings could provide valuable insights. Areas of investigation might include the differing effects of amide versus ester-type anesthetics, a comparison between opioids and local anesthetics in achieving sensory and motor blocks, and the influence of adjunctive medications—such as sodium bicarbonate, dexmedetomidine, and clonidine—on the onset and peak effects of sensory and motor blocks.

Conclusion

According to the results from various studies, scorpion sting is one of the substances that induces resistance to some of the medications used for local anesthesia. Patients with a history of scorpion stings show inadequate block or block failure while the frequency and history of stings are associated with stronger resistance. With scorpion venom being proven as one of the compounds with a high impact on anesthesia, anesthesiologists should keep a history of scorpion stings in mind in areas where scorpion sting cases happen frequently.

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