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Do Previous Multiple Scorpion Bites Produce Resistance to Local Anesthetics Administered Via Repeated Subarachnoid and Epidural Blocks? A Case Report and Review of Available Evidence

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Abstract

Introduction: Failure to achieve a subarachnoid block, even after a second attempt, and the inability to activate epidural analgesia, despite a properly placed catheter, can be both frustrating and perplexing. This case presents a situation where these incidents occurred, and two well-conducted attempts at a subarachnoid block and a properly placed epidural catheter block were unable to produce surgical anesthesia.

Case Presentation: A 55-year-old female, classified as American Society of Anesthesiologists (ASA) grade II, was scheduled for a total abdominal hysterectomy with bilateral salpingo-oophorectomy. After adequate pre-operative preparation, an epidural catheter was inserted on the morning of surgery, followed by a subarachnoid block with all the proper precautions, which completely failed. After waiting for 10 minutes, the epidural block was activated with a local anesthetic mixture. To our surprise, it also did not produce any desirable effect, so the subarachnoid block was repeated, which again failed to produce any clinical block. Consequently, the surgery had to be conducted under balanced general anesthesia. Recalling previous experience and evidence, a history of scorpion bites was elicited. The patient had a history of multiple encounters (five) and was from a geographical area known to be endemic for scorpions.

Conclusions: This case represents another instance of developing resistance to the effects of local anesthetics after exposure to scorpion venom. We believe there is a strong correlation between previous scorpion bites, the number of bites, and the duration between the most recent bite and the development of resistance to local anesthetic agents (LAAs). From a detailed search, it was evident that enough clinical evidence has emerged to irrefutably support this proposal.

Keywords: Anesthetics Local, Resistance, Anesthesia Spinal, Anesthesia Epidural, Failure, Scorpion-Stings, Multiple/Recent

1. Introduction

Resistance to the effects of local anesthetic agents (LAAs) is a well-reported phenomenon by many authors (1-5). In fact, in an extensive review on 'failed spinal,' Fettes et al. have attempted to elaborate on the multiple aspects of the issues involved in spinal failure, including resistance to LAAs (6).

None of these reports mention any possible correlation between the development of resistance or failure of LAAs due to previous single or multiple scorpion bites, possibly because they never encountered this problem. Since this phenomenon was first reported in 2012 (7), with an interesting case report followed by another case report (8) and a conclusive case-control study (9) along with a proposed hypothesis (10), there have been some additional case reports (11, 12) and three studies (13-15) from India and abroad (Turkey) (11) that corroborate and support the idea of this phenomenon. It appears that there may be a substantial correlation between the development of resistance to the action of LAAs and scorpion bites, especially multiple bites or bites that occurred in the recent past.

Recently, we encountered such a case, which vividly reminded us of the same phenomenon with very striking features. We are reporting it here.

2. Case Presentation

A 55-year-old female weighing 49 kg was admitted to our Gynecology ward in January 2023 with post-menopausal bleeding. In December 2022, she had undergone dilatation and curettage (D&C) under general anesthesia (GA) at our hospital for similar complaints, but to no avail. She reported having had an abdominal tubal ligation under local anesthesia 18 years earlier, which was uneventful. There was no history of COVID-19. A total abdominal hysterectomy with bilateral salpingo-oophorectomy and intra-operative frozen section biopsy (TAH-BSO & proceed) was planned. The pre-anesthetic examination was essentially normal, except for anemia (hemoglobin of 9.3 g/dL), an ECG showing poor progression of R waves, and a chest radiograph indicating mild emphysematous changes. She was classified as American Society of Anesthesiologists II (ASA II) and was cleared for the proposed surgery under combined spinal-epidural (CSE) anesthesia.

On the morning of the planned surgery, the pre-anesthesia review found everything status quo, so the original decision for CSE was confirmed. A 20-gauge intravenous line was in place and running. Routine monitoring showed normal parameters.

At 11:30 a.m., with the patient in a sitting position and after thorough aseptic precautions, an epidural catheter was placed using an 18-gauge Tuohy needle with loss of resistance. The catheter was inserted to a length of 8.5 cm, and its placement was confirmed by the movement of the saline column in the catheter.

At 11:35 a.m., a subarachnoid block was carried out using a 25-gauge Quincke needle at the L3-4 interspace. After achieving free flow of cerebrospinal fluid (CSF), a drug mixture of 3.2 mL of 0.5% hyperbaric bupivacaine and 0.2 mL (30 μg) of clonidine, totaling 3.4 mL, was injected after confirming free CSF flow. The patient's position was changed to supine immediately, and assessment with the pin-prick method for sensory block and the Bromage scale for motor blockade was started. Despite waiting for more than 5 minutes, there was not even the slightest change in sensation or motor power in either of the lower limbs. Thus, the decision was made to activate the epidural.

At 11:45 a.m., after confirming the catheter was not intravascular with 3 mL of 2% lignocaine with adrenaline, an additional dose of 6 mL of plain bupivacaine (0.05%) was injected into the epidural space.

To our utter dismay, even after waiting for 10 minutes, there was no change at all in the situation, with no sensory or motor block achieved.

At 11:55 a.m., the patient was made to sit up again, and in the lower interspace, after achieving free flow of CSF, another drug mixture of 3 mL of 0.5% bupivacaine and 0.15 mL of clonidine (25 μg), totaling 3.2 mL, was injected. After waiting another 10 minutes with no neuraxial block achieved (the patient winced at the bite of the tooth forceps), it was decided to switch to GA.

At 12:05 p.m., using 100 mg of propofol, 100 mg of succinylcholine, a cuffed endotracheal tube no. 7.5, a gas mixture, sevoflurane, atracurium, and intermittent positive pressure ventilation (IPPV), balanced GA was achieved. Intra-operatively, the hemodynamic parameters were more or less stable, with only a mild fall in blood pressure and mild bradycardia (less than 10% of baseline) that were easily managed with crystalloids. The surgery was completed uneventfully in nearly two hours.

In the post-anesthesia care unit (PACU), the patient was examined and found to be conscious, well-oriented, and hemodynamically stable. The motor power in the left lower extremity was Bromage grade II. There was near-total loss of sensation up to T8-10. The VAS score was 0. The patient was drowsy but arousable.

In the PACU, recalling previous evidence and the association between scorpion bites and local anesthetic resistance, we asked the patient if she had ever been bitten by a scorpion. To our surprise, she reported having been bitten by scorpions five times in the past, starting nearly 16 years ago and most recently about 8 months ago. Although she currently lives in Pune, she is originally from a village near Chiplun, in the Ratnagiri district of the Konkan area in the Western Ghats of Maharashtra, India, which is highly endemic to scorpions. She encountered these interactions with scorpions during her farming work. Upon further inquiry about the use of local anesthesia in her previous surgery (tubectomy), it was noted that this surgery took place 18 years ago, before any scorpion bites, and the local anesthesia was effective with no pain during the procedure. All her encounters with scorpions occurred in the last 16 years. For the D&C, she was given GA, so everything was uneventful.

The patient had an uneventful hospital stay and was discharged without any sequelae.

3. Discussion

With the help of previously reported evidence on the failed effects of LAAs administered via various routes (neuraxially: Both intrathecal and epidural, peribulbar block, wrist block, and supraclavicular block), a tangible

association has been well established between two entities: A history of scorpion bites in the past and the development of resistance to the action of LAAs in the future (7-10). Since then, many authors have also reported this phenomenon (11, 12). There are even three studies (13-15), the most recent one from 2023 (15), that emulated the reported methodology and confirmed the earlier conclusions and the proposed mechanism.

In our patient, the failure of both subarachnoid blocks and the epidural block is highly suggestive. There can be no doubt about the placement of the epidural catheter or the deposition of the drug mixture in the subarachnoid space. The effects of LAAs were not identifiable, but the intraoperative hemodynamic effects of the addition of the α2 agonist clonidine (total of 55 μg) were obvious. Even postoperatively, she exhibited persistent effects, including continued analgesia and sedation, but with a Bromage score of 2 (indicating incomplete motor blockade due to partial/failed LAAs). The mechanism of action of alpha 2 agonists is believed to involve binding to alpha 2 receptors at the substantia gelatinosa (Rexed lamina II). This action "closes" the gate at the dorsal horns to noxious stimuli transmitted by Aδ and C fibers, thereby producing analgesia. This process involves hyperpolarization (mediated through a G1 protein-controlled gating mechanism) and the regulation of calcium channels (mediated through G0 protein-controlled, N-type voltage-gated channels) as well as the inhibition of the release of nociceptive humoral transmitters like Substance P (16-22). This may explain the persistent analgesia in the postoperative period (VAS 0) despite the absence of motor blockade.

Scorpion venom is highly antigenic, generally an acidic liquid mixture of chemicals, including peptide enzymes and salts/amines that act as neurotoxins. There are two components, α and β toxins, which have specific targets: Voltage-gated sodium channels (Navs). The α component of scorpion venom mainly acts on IV-S3, while the β component is thought to act on S4, ultimately inhibiting impulse propagation and causing spastic paralysis (23).

It has already been postulated that after initial envenomation, following an acute reaction at the voltage-gated sodium channels (Navs) on the peripheral nerves (the site of action of toxins in the venom), the patient recovers and returns to a normal life. However, over time, especially with multiple and/or recent exposures, antibody formation might occur (7-10). Coincidentally, LAAs have the same site of action. They are believed to act specifically at the voltage-gated sodium channel. Structurally, the sodium channel comprises alpha, beta-1, and beta-2 subunits. Four homologous domains (I-IV) are situated in the alpha subunit, and each of these domains has six transmembrane segments (S1-S6). The main site of action of LAAs is believed to be at the alpha subunit-domain IV and the sixth segment (alpha-IV-6) (24). Logically, the mechanism of resistance to LAAs appears to be related to alpha-IV-6 (25).

Therefore, if a patient with a history of previous scorpion bites is otherwise leading a normal life and is exposed to an LAA, the LAA may not bind to the target site, possibly due to antibody-mediated competitive antagonism for the same site, leading to the failure of the LAA. This seems to be a highly suggestive mechanism because, in our patient, before exposure to the scorpion bite, local anesthesia was successful during a tubectomy performed 18 years ago.

A detailed description of the proposed mechanism of action can be found in the literature already published (7-10). It is noteworthy that all subsequent reports after the initial ones (7-10) also agree that the site of resistance may be sodium channels (11-15) and possibly antibody-mediated (12-14).

Many other causes of resistance to LAAs have been reported due to mutations/modifications or atypical characteristics of these sodium channels (24, 25). Recently, a case series has also confirmed these findings of resistance development to certain local anesthetics like bupivacaine, citing previous reports and suggesting ropivacaine as a possible alternative for patients with a history of scorpion bites and the development of resistance to LAAs (26).

It is very interesting to note that the geographical area of our patient, a rural area near Chiplun (Ratnagiri district/the Western Ghats), is highly endemic to various species of scorpions, such as *Isometrix tamhini* and *Isometrus amboli* (Family Buthidae), which are named after the Tamhini Ghat and Amboli Ghat (27). Therefore, scorpion bites during the course of daily work are considered routine and are not usually mentioned by patients unless specifically asked, as was the case with our patient.

3.1. Conclusions

The obvious deductions that can be drawn from this case are: 1, resistance to LAAs, though rare, is a real phenomenon with multiple etiologies and pathologies; 2, a previous scorpion bite appears to confer resistance to LAAs. The extent of this resistance, which can manifest as a complete failure, partial or incomplete block, or selective sensory or motor block, depends on how many times the person has been bitten and how

recently. The more frequent and recent the bites, the more severe the resistance; 3, considerable supportive evidence has been emerging since this was first reported; 4, in endemic areas, it would be worthwhile to ask about a history of scorpion bites during the pre-anesthesia check-up; 5, more molecular-level research in this area is needed to confirm the hypothesis.

Footnotes

Authors' Contribution: M. M. P., conceived and designed the evaluation and drafted the manuscript, and finalized the manuscript; K. K. and R. V., actually conducted the case under the supervision of M. M. P. and helped to draft the manuscript; M. M. and M. M. P., did most of the literature search and finalized the manuscript; M. M. and K. K., revised the manuscript. All authors read and approved the final manuscript.

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Informed Consent: Although, this was a anesthetic management of a routine case, the informed consent was already obtained. In addition, the consent without disclosing the identity/ photograph of the patient, was obtained.

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