Case Report

# Does scorpion bite lead to development of resistance to the effect of local anaesthetics?

**Address for correspondence:**
Prof. Minnu Mridul Panditrao, Department of Anaesthesiology and Intensive Care, Padmashree Dr. Vithalrao Vikhe Patil Foundation's Medical College and Hospital, Vilad Ghat, Ahmednagar, Maharashtra - 414 111, India.
E-mail: drmmprao1@gmail.com

**Access this article online**

Website: www.ijaweb.org

DOI: 10.4103/0019-5049.104582

Quick response code

*Minnu Mridul Panditrao, Mridul Madhav Panditrao, Mohd. Irfan Khan[1], Nikhil Yadav[1]*

**Department of Anaesthesiology and Intensive Care, Padmashree Dr. Vithalrao Vikhe Patil Foundation's Medical College and Hospital, Vilad Ghat, Ahmednagar, [1]Department of Anaesthesiology and Critical Care, Padmashree Dr. D.Y. Patil Medical College, Pimpri, Pune, Maharashtra, India**

## ABSTRACT

A patient posted for vaginal hysterectomy was administered subarachnoid block, which failed, so was repeated in one space above. The block failed again, after waiting for 30 min. Patient gave a history of scorpion bite twice, once at the age of 17 years on her right foot and again about 8 months back. Thereafter, balanced general anaesthesia was given. On eighth post-operative day, after explaining about her possible special condition (?Resistance to local anaesthetic agents), the patient was given left median, ulnar and radial nerve blocks at the wrist and local infiltration near the anatomical snuff box. There was neither sensory nor motor block. The scorpion venom is known to affect the pumping mechanism of sodium channels in the nerve fibres, which are involved in the mechanism of action of local anaesthetic drugs, it may be responsible for the development of 'resistance' to the action of local anaesthetic agents.

**Key words:** Resistance to local anaesthetics, scorpion bite, various routes

## INTRODUCTION

Resistance to or "failure to achieve" the block by local anaesthetic agents by various routes is an uncommon but a known phenomenon. There are reports of "not able to achieve" the optimum sensory/motor effect when given either via neuraxial, peripheral nerve blocks or as local infiltration, where, because of lack of any plausible explanation, the absence to achieve the block had to be attributed to the so-called "failure" of local anaesthetics.[1] In a recent review, various factors/causes have been considered to be responsible for this; however, these may not be applicable to certain particular cases.[2] Even genetic factors like being a Redhead, i.e. carrying a variant of the melanocortin-1 receptor (MC1R) gene, can lead to resistance to not only local anaesthetics like novocaine and lidocaine but may make them resistant to the effects of inhalational anaesthetic agents like desflurane.[3-5] In spite of being in practice for more than a century and having been/is being administered to millions of patients every year, this phenomenon is known to happen occasionally, even in expert and skillful hands. This in itself may be misinterpreted as "technical" or "skills" failure on the part of the anaesthesiologist, giving him/her low morale and embarrassment while facing his/her own and surgical colleagues and also the patient. As such, it might not be his/her mistake, but the sheer coincidence of the patient having these yet unknown factors might be responsible for this phenomenon.

## CASE REPORT

A 65-year-old multiparous female with grade IV procedentia, cystocele, rectocele and enterocele was admitted for vaginal hysterectomy and pelvic floor repair. On pre-operative evaluation, she gave history of hypertension, controlled with Tab. Amlodipine 2.5 mg once a day. Her general physical examination was normal and she was Mallampati grade II. All the laboratory investigations, chest X-ray, ECG and two-dimensional echo cardiography were within normal limits. She was accepted for vaginal hysterectomy and pelvic floor repair as ASA grade II.

**How to cite this article:** Panditrao MM, Panditrao MM, Khan MI, Yadav N. Does scorpion bite lead to development of resistance to the effect of local anaesthetics?. Indian J Anaesth 2012;56:575-8.

Inside the operation room, intravenous infusion of 5% Dextrose in normal saline was started with a 20 gauge indwelling intravenous cannula. Three-parametric monitoring including ECG, oxygen saturation ($SpO_2$) and non-invasive blood pressure (NIBP) was started. Under all aseptic precautions, lumbar puncture was performed at the level of the L3-4 interspace with a 26 gauge Quincke's needle in sitting position. After confirming the free flow of cerebrospinal fluid (CSF) on aspiration, 3.5 mL 0.5% of hyperbaric bupivacaine was injected into the subarachnoid space. Thereafter, the patient was made supine with 10 degrees head down tilt. In spite of waiting for 20 min, the patient did not show any signs or symptoms of sensory block, as confirmed by pinprick method or of motor block, as confirmed by movements of lower limbs or toes.

The patient was made to sit up again and spinal anaesthesia was repeated. This time, it was given by a senior consultant with >25 years of professional experience at L2-3 interspace. Again, 3.5 mL of 0.5% hyperbaric bupivacaine of a different batch and brand was injected after confirming the free flow of CSF on aspiration. The patient was made supine and 20 degree head down tilt was given. To our dismay, this time also, there was no sensory or motor block in spite of waiting for 30 min. The patient also did not show any signs of autonomic block, i.e. hypotension, bradycardia or even tachycardia. Motor power in both the lower limbs was grade IV and there was no sensory block at any dermatomal level.

At this point, after very specific inquiry into past history, the patient gave history of scorpion bite twice; first, at the age of 17 years, she had scorpion bite on her right foot and the second time, she had scorpion bites on her face, neck, right arm and forearm about 8 months back (this happened when she was sleeping on the floor in her farmhouse).

Thereafter, it was decided to give standard balanced general anaesthesia for the procedure. The patient was given Inj. Glycopyrrolate 0.2 mg IV, followed by Inj. Butorphanol 1 mg IV. Induction was done with Inj. Propofol and Inj. Rocuronium and, after intubation, anaesthesia was maintained with oxygen and nitrous mixture, isoflurane and controlled ventilation. The surgery lasted for 105 min, and was uneventful. After the end of surgery, residual paralysis was reversed with Inj. Neostigmine and Glycopyrrolate and the patient was extubated after adequate recovery of respiration, laryngeal and pharyngeal reflexes. In the immediate post-operative period, after recovery of consciousness and orientation, she did not show signs of any residual/delayed neuraxial block. The patient was followed up in the post-operative period for the next 48 h, which was uneventful.

On the eighth post-operative day, the patient was called to the operation theatre accompanied by her daughter and a gynaecology resident. After explaining them about her possible special condition (? Resistance to local anaesthetic agents) and obtaining informed consent, the patient was administered peripheral nerve blocks of left median, ulnar and anterior interosseous branch of radial nerves at the level of wrist (wrist block) using 0.5% bupivacaine (total volume 12 mL). Also, local infiltration of the skin near the anatomical snuff box of the left arm using 2% xylocaine with adrenaline (total volume 3 mL) was carried out. Confirming our suspicion, there was neither sensory nor motor block after these injections. Even the infiltration did not produce any perceptible sensory loss. The patient was observed in the recovery room for the next 2 h and then sent back to the ward.

On the $10^{th}$ post-operative day, after satisfactory recovery from the surgical procedure, she was discharged from the hospital.

## DISCUSSION

Spinal anaesthesia is not a 100% certain successful technique. Failure rates of 0.72-16.0% have been reported.[6-8] The causes of some failures may be due to technical difficulty and inability to identify and access the subarachnoid space or to inject the correct drug in appropriate dosage, which is obvious at that moment and is understandable. The explanation for spinal block failure that occurs despite the apparent technically correct injection of the correct drug can be mystifying. As a result, true local anaesthetic resistance is difficult to diagnose, and may be greeted with skepticism.[9] However, because local anaesthetics work via the sodium channel, it is theoretically possible that mutations in this channel might lead to differing responses to these medications.[10]

Recently, in 2009, the subject of failed spinal anaesthesia enjoyed its first large review, "Failed spinal anaesthesia: mechanisms, management, and prevention" by Fettes.[11] A recent case report by Hoppe of four failed obstetric spinal blocks gives a

good summary of anatomical reasons and ligamentous cysts that can cause technical failure.[12]

Causes of failed spinal anaesthesia can be classified as[2]

1. Successfully injected drugs that are maldistributed relative to the needs of the planned surgery
2. Unrecognized failed injection of drug, partial or total
3. Technical failure to enter the subarachnoid space, with no drug injection
4. Drug errors, i.e. wrong drugs and inappropriate additives
5. Local anaesthetic resistance
6. Pseudo block failure due to excessive expectations for speed of block onset
7. Subdural injection of a spinal dose is conceptually a possible cause of spinal block failure, but has never been reported, recognized or studied in this context of small-volume injections.

An extensive literature search has revealed isolated case reports of local anaesthetic resistance, mainly in dental practices where repeated procedures are more likely to happen. There is one reported pilot study conducted in The Pain Centre in Florida evaluating the prevalence of apparent local anaesthetic resistance to mepivacaine, lignocaine and bupivacaine. Of the 1198 patients interviewed, 250 were tested. Ninety patients (7.5% of the total patients) were found to be hypoesthetic only to mepivicaine, and an additional 43 (3.8%) only to lignocaine. The rest were hypoesthetic to all or bupivacaine.[13]

In another study, the authors have reported that complex regional pain syndrome (CRPS) is sometimes treated with epidural and/or spinal local anaesthetic blockade as part of a comprehensive treatment plan. They have identified subgroups of patients exhibiting different patterns of ineffective local anaesthetic blockade, which could not be explained by technical failure of needle or catheter positioning. Based on these observations, they have attempted to characterize the clinical features of these cases that appear to involve resistance to local anaesthetic blockade. Central neuroplasticity has been implicated in response to local anaesthesia in patients with phantom limb pain and in animal and human models of tachyphylaxis. Related mechanisms may be involved in patients with apparent local anaesthetic resistance, and may suggest future directions for therapeutic interventions.[14] One of the postulated mechanisms for local anaesthetic resistance is receptor mutation associated with sodium channel abnormalities. An atypical receptor site might result from genetic variation in the amino acid sequence within the sodium channel. Specifically, the sodium channel has been shown to consist of alfa, beta-1 and beta-2 subunits. The alfa subunit involves four homologous domains (I-IV), and each of these domains is made up of six transmembrane segments (S1-S6). Local anaesthetic action is believed to be due to an interaction with the sixth segment of domain four of the alpha subunit (IV-S6), involving sites of phenylalanine and tyrosine amino acid residues.[15] Therefore, it is possible that genetic variation that alters the site of action as stated above can be the cause of resistance to local anaesthetics.[16]

Scorpion bites are a relatively common phenomenon in subtropical countries like India. The clinicians do not give much importance to the past history of the scorpion bite as a relevant and consequential factor. Especially, if the patient has come for unrelated medical/surgical condition, just a passing mention to this fact may be recorded and forgotten. An average scorpion's venom contains numerous toxins, biogenic amines, enzymes, salts, unidentified substances and water. Based on the composition, the toxins have been divided into two main groups; the Buthidae and the Chactoids. For clinicians, Buthidae is of more significance as these toxins are known to affect sodium ion channels, potassium ion channels and calcium ion channels with regards the electrolyte balance. Disturbance of electrolyte balance can affect the following.

Sodium and calcium permeability affects the heart. Sodium and potassium affect the nerve transmission and cell membrane integrity. Sodium affects the homeostasis by kidney. Calcium affects the muscles and is an important secondary messenger.[17]

The neuromuscular intoxication by scorpion venom may be due to its ability to act on exposed fibres or on muscles directly or through motor nerves. Because an intact nerve trunk appears to be impermeable to the venom, the venom makes contact with the nerve tissue at the exposed pre-synaptic terminals at the neuromuscular junction. The resulting muscular twitchings and fibrillations may be due to release of the transmitter substance. It appears that scorpion neurotoxins (which are low molecular weight, thermostable, basic proteins) possess the general

ability to depolarize excitable membranes. This is due to an increase in the sodium permeability of the resting membrane and reduction of the rate and amount of sodium inactivation. It is suggested that scorpion venom may modify the sodium-pumping mechanism within fibres as well as affecting the passive and active sodium permeability systems. It is the antigenic nature of scorpion venom that makes it more significant as it may evoke a very potent antigen-antibody response.

We have actually, in the past, experienced a similar apparent "resistance" in some patients (with history of scorpion bite) as happened in this case, but did not give any significant importance to it. The confirmation of inability to block even the three peripheral nerves, i.e. median, ulnar and anterior interosseous branch of radial as well as the complete failure of local infiltration, highlights the possibility of development of "resistance" to local anaesthetics, and appears to be the most likely and plausible explanation of "failure of spinal block." For the sake of argument, one may put forward, a hypothesis that, she might have been inherently resistant to the local anaesthetics as such, because there is no past history of the use of local anaesthetics before the occurrence of scorpion bite. This may be a remote possibility, but one has to accept the irrefutable fact that, this woman had been bitten by a scorpion not once but two times and that also at multiple sites. This might have led to the development of antibodies against the scorpion venom, which may be circulating even at the time of administration of local anaesthetics and may have produced competitive antagonism with them at the "receptor site", viz that particular component of sodium channels (sixth segment of domain four of the alfa subunit (IV-S6)), where the local anaesthetics are supposed to act.[15] The second exposure might have further augmented this response, making her even more "resistant" to the effect of local anaesthetic agents.

The literature search also suggests that there is enough evidence, that irreversible inhibition of scorpion venom may be partially protected by bupivacaine, suggesting a common binding site.[18] This also goes in favour of our hypothesis that the previous envenomation by scorpion bite may actually interfere in the action of the local anaesthetics due to this commonness of the binding site.

## CONCLUSION

We are convinced about the hypothesis, that "single/repeated scorpion bites" may cause development of resistance to the local anaesthetic drugs used to achieve blocks by various routes!!

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**Source of Support:** Nil, **Conflict of Interest:** None declared