Case Report

Suspected local anesthetic resistance after intrathecal, perineural, intraarticular and subcutaneous injections: a case report

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Background: Local anesthetic (LA) resistance is an exceedingly rare phenomenon. Incidence is unknown given the rarity of disease. Often, inadequate response to LA can be attributed to many factors including suboptimal dosing, maldistribution, or poor procedural technique. However, in the absence of these technical factors, true LA resistance can be attributed to mutations in the voltage gated sodium channel and is strongly associated with hypermobility conditions such as Ehlers Danlos and muscular dystrophies such as Emery-Dreifuss. There have also been reports describing LA resistance after scorpion bites, although the underlying mechanism for this type of resistance is unknown. We aim to present a case of suspected LA resistance in the setting of multiple failed LA delivery.

Case Description: In this case report, we describe a patient with suspected LA resistance after failed intrathecal, perineural, intraarticular and subcutaneous delivery of LA. Our patient was unresponsive to three different LAs at varying doses.

Conclusions: Patients with failure to achieve adequate anesthesia with more than one route of LA administration should be evaluated for LA resistance. A thorough medical history and physical examination, along with a focus on identifying prior LA failure such as with dental procedures, and physical examination findings suggestive of connective tissue disorders may help establish the diagnosis with confirmatory genetic testing.

Keywords: Case report; local anesthetic resistance (LA resistance); pain management; nerve block; spinal anesthesia

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Introduction

The incidence of resistance to local anesthetics (LAs) is unknown, although reported cases are rare. Most inadequate responses to LA occur due to technical factors, such as improper needle or catheter positioning, maldistribution of the anesthetic agent, or suboptimal dosing of anesthetic drugs. However, several case reports have revealed instances of inadequate response to LA despite proper technique, thus suggesting true resistance (1-8).

Resistance to LA may be due to mutations in the voltage-gated sodium channels by which LA induces nerve blockade. *In vivo* models demonstrate that specific mutations near the sodium channel intracellular pore region can decrease inactivated channel's affinity for LA by up to 21-fold (9,10). Similar findings have been reported in human studies; after failure of an ultrasound (US)-guided brachial plexus nerve block, a patient and their immediate family underwent whole exome sequencing. Three family members with LA resistance possessed a genetic variant in the voltage-gated sodium channel which was not present in the unaffected family member (1,11). Therefore, while uncommon, compelling evidence supports the existence of true LA resistance, and further research is warranted to optimize acute pain management in this patient population. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-17/rc).

Highlight box

Key findings

- We describe a patient with suspected local anesthetic (LA) resistance after failed intrathecal, perineural, intraarticular, and subcutaneous delivery of LA in the absence of technical error, maldistribution, inadequate dosing, or inactive LA solution.
- Patient has a history of refractory, intense pain with dental procedures.
- Patient has a seizure disorder that is well-controlled with two anti-epileptic drugs, both of which work through central nervous system voltage-gated sodium channel blockade.

What is known and what is new?

- Most inadequate responses to local anesthesia occur due to technical factors.
- Resistance to local anesthesia is rare. One possible cause for resistance includes mutations to voltage gated sodium channels.
- We hypothesize this patient had a voltage gated sodium channel mutation that serves as a common etiology for both her epilepsy and resistance to LAs. This has not been previously reported in literature. Alternatively, she may have upregulated sodium channel receptors or competition for binding sites due to chronic sodium channel blockade.

What is the implication, and what should change now?

- Clinical tools to identify patients at risk for LA resistance prior to attempted procedures may prove useful, so that alternative anesthetic strategies can be employed.
- Further studies investigating overlapping roles of LA resistance and epilepsy and/or antiepileptic drugs may be warranted if other cases of LA resistance in such patients emerge.

Case presentation

A 55-year-old, 70 kg female presented for right knee arthroplasty and total replacement. Past medical history included obstructive sleep apnea (OSA) with nightly continuous positive airway pressure (CPAP), remote cerebrovascular accident (CVA) with no residual sensorimotor or cognitive deficits, and seizures well-controlled with lamotrigine and lacosamide with no seizures in several years. Surgical history included a bilateral tubal ligation, and she reported no prior issues with general anesthesia. Family history was noncontributory. Social history was pertinent for social drinking and smoking which she quit the year prior. Daily medication usage included lamotrigine, lacosamide, sertraline, and lisinopril-hydrochlorothiazide. Physical examination was unremarkable. The planned anesthetic for her surgical procedure was primary spinal anesthesia with supplementary propofol infusion for sedation.

Upon arrival in the operating room the patient was connected to standard American Society of Anesthesiology (ASA) monitors. Vital signs were within normal limits. Midazolam 2 mg intravenous (IV) was given for anxiolysis. An experienced attending anesthesiologist accessed the intrathecal space percutaneously between the L3–L4 vertebrae using anatomic landmarks for guidance. Placement was verified by the presence of free-flowing cerebrospinal fluid (CSF), and a characteristic birefringent swirl of CSF aspirated into the syringe of LA. A 1.6-mL 0.75% hyperbaric bupivacaine in dextrose with 100 mcg epinephrine was injected into the spinal space. The patient was immediately placed in the supine position. A mild sympathectomy was noted after the administration of spinal anesthesia. Nasal cannula with end tidal carbon dioxide ($ETCO_2$) was placed on the patient and a propofol infusion was started. Despite moderate sedation and spinal, the patient reacted to the surgical incision, and within five minutes it became clear that she would not tolerate the

surgical procedure and she had no motor blockade. She was converted to general anesthesia with a supraglottic airway and inhaled sevoflurane for the remainder of the case. Other intraoperative medications included 2 mg cefazolin, 2,000 mg tranexamic acid, 8 mg dexamethasone, 1 mg hydromorphone, 4 mg ondansetron, and 10 mg labetalol. The surgeon injected 30 mg ketorolac combined with 60 cc of 0.2% ropivacaine into the soft tissues and periosteum of the knee at the conclusion of the procedure.

In the post anesthesia care unit (PACU), the patient complained of 10/10 pain that was minimally responsive to 10 mg oxycodone, 200 mcg fentanyl and 2 mg hydromorphone. The patient was started on a multimodal pain plan that included acetaminophen, oxycodone, celecoxib, cyclobenzaprine, and hydromorphone. On postoperative day #1, the acute pain service was consulted for failure of oral and IV pain medications to adequately provide post-surgical analgesia. Therefore, a peripheral nerve block was recommended, and the patient consented to proceeding with the procedure.

US imaging was used to identify the saphenous nerve in the adductor canal. The superficial tissues and skin at the access site were then infiltrated with 1% lidocaine, which did not result in the expected anesthesia. A 20-mL 0.5% ropivacaine was then injected into the space surrounding the saphenous nerve. A catheter was then positioned in the space, and placement was confirmed sonographically by injection of air through the catheter, demonstrating catheter placement directly under the nerve. No change in pain intensity was appreciated, with an unchanged pain score at 5, 20 or 60 minutes after placement. At the 90-minute mark, 10 mL of 2% lidocaine was administered perineurally through the catheter with no change in pain intensity at the 10- or 15-minute mark as reported by the patient. Physical examination revealed intact sensation to cold and pinprick in the saphenous distribution. The patient was therefore started on an IV ketamine infusion at 10 mg/h for 24 h after which the patient reported improvement in her pain, and she was discharged to home.

On interview after failure of both her spinal anesthetic and peripheral nerve block, the patient recollected intense pain during dental procedures even when given additional numbing medications by dental providers. The patient denied any history of connective tissue disorders, scorpion bites, and to her knowledge, no one in her immediate family had issues with LAs. Genetic testing for known mutations associated with LA resistance was offered, but the patient declined stating she was “too old now”. However, she was very appreciative for the team and our efforts in getting her pain under control with the aid of ketamine.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Despite receiving correct placement and adequate dosing of spinal anesthesia, subcutaneous anesthesia, intraarticular anesthesia, and an adductor canal nerve block with three different types of LAs at different concentrations, this patient continued to have uncontrolled pain with no significant effect observed from any of the LA. LA failure generally can be attributed to improper catheter positioning, maldistribution of the anesthetic agent, suboptimal dosing of anesthetic drugs, inactive LA solution, or rarely, LA resistance. Steps to confirm the absence of technical error were performed in each procedure. The presence of free-flowing CSF and birefringence during spinal anesthesia administration, direct visualization by the surgeon for subcutaneous and intraarticular local anesthesia, and US visualization of adequate LA distribution around the saphenous nerve during the nerve block all suggest appropriate administration. Furthermore, two attending anesthesiologists and one senior resident performed her spinal anesthesia and adductor canal nerve block, all of whom have ample regional anesthesia experience. For these reasons, technical error is a very unlikely cause for the failure of multiple LA techniques.

Although this patient required greater doses of systemic analgesia, underdosing is not likely the cause for the multiple LA failure in the patient. For her spinal anesthesia, she received 1.6 mL 0.75% hyperbaric bupivacaine in dextrose (12 mg bupivacaine). For her intraoperative subcutaneous and intraarticular injections, 1.7 mg/kg ropivacaine was given. She received 1.4 mg/kg ropivacaine 0.5% for her initial adductor canal nerve block, with an additional 2.8 mg/kg lidocaine 90 minutes later. These doses should all be adequate to provide effective analgesia. The patient had no sensory block or reduction with intact sensation after each of the three attempts of local anesthesia.

Although rare, an LA solution may come inactive and

cause LA failure. However, given that three different drugs at various doses from at least 5 different vials were used, inactivation of the LA solution is highly unlikely.

With three failed local anesthesia responses in the absence of technical error, maldistribution, inadequate dosing, or inactive LA solution as well as a history of refractory, intense pain during dental procedures, this patient was suspected to have LA resistance. Although this patient does not have commonly cited risk factors for LA resistance such as a connective tissue disorder, family history, or scorpion bite history, she interestingly does have a seizure disorder that is well-controlled with two antiepileptic drugs, both of which work through central nervous system voltage-gated sodium channel blockade (lamotrigine and lacosamide). One cited mechanism of hereditary LA resistance is mutations in voltage-gated sodium channel receptors (1,10,12,13). Although the intended clinical effects of LA and antiepileptic drugs are different, both classes of drugs share a common mechanism of binding to the central cavity in the core of voltage-gated sodium channel alpha subunits, and both classes lack sodium channel subtype specificity (13,14). This introduces two potential hypotheses for this patient. First, it is conceivable that a sodium channel genetic variation serves as a common etiology for both her epilepsy as well as her resistance to LAs, though this has not been previously reported in the literature. Alternatively, it seems conceivable that the mechanism for LA resistance could be upregulated sodium channel receptors or competition for sodium receptor binding sites due to chronic sodium channel blockade.

Conclusions

We describe a patient with suspected LA resistance after failed intrathecal, perineural, intraarticular, and subcutaneous delivery of LA in the absence of technical error, maldistribution, inadequate dosing, or inactive LA solution. Patients with failure to achieve adequate anesthesia with more than one route of LA administration should be evaluated with a thorough medical history and physical examination, with a focus on identifying prior LA failure such as with dental procedures, and physical examination findings suggestive of connective tissue disorders. Genetic testing may be considered for many patients, particularly those with a positive family history. Future research is needed to further investigate mechanisms behind LA resistance and elucidate inheritance patterns. Clinical tools to identify patients at risk for LA resistance prior to attempted procedures such as spinal anesthesia may prove useful, so that alternative anesthetic strategies can be employed. Further studies investigating overlapping roles of LA resistance and epilepsy and/or antiepileptic drugs may be warranted if other cases of LA resistance in such patients emerge.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-17/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-17/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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