breakthrough pain is supported by moderate certainty evidence and can be used in the appropriate population.

4. For palliative therapies and the treatment of neoplastic pain, the evidence is still limited, as it is for the treatment of headache, but there is evidence of considerable interest.

The optimal analgesic dosage of ketamine varies widely in the literature, ranging from 0.15 to 0.5 mg/kg. However, doses above 0.3 mg/kg can lead to psychomimetic symptoms, and 0.5 mg/kg is considered a subdissociative dose and is associated with a higher rate of adverse events. As a result, many authors define safe and effective analgesic dosing as 0.15–0.3 mg/kg bolus, 0.15–0.3 mg/kg/h continuous infusion, 0.5–1 mg/kg intramuscular administration, and 1 mg/kg intranasal administration. Oral administration of ketamine is not standardized, but doses of 0.5 mg/kg every 12 h are considered effective. Other possible routes of administration include transdermal (25 mg/24 h), subcutaneous (0.05–0.15 mg/kg/h), and rectal (10 mg/kg).

The administration method can be tailored to the clinical setting: Continuous infusion administration (up to 100 hours) takes advantage of the increased levels of ketamine metabolites and their analgesic and antidepressant properties. Infusions (up to 100 h) resulted in a sustained analgesic response of 4 to 8 weeks, while infusions of 12 to 24 h resulted in a reduced but stable response of 7 to 10 days.

Ketamine is an excellent drug for the treatment of severe pain in acute cases, but also has remarkable benefits in chronic pain infusions. Unfortunately, there is currently no clinical evidence to predict individual patient responses. Identifying clinical factors that can predict a patient’s response to ketamine will help clinicians determine the most appropriate treatment option. So rigorous research is still needed.

Given the opioid crisis, such studies are more urgent than ever. Future research should also investigate ketamine enantiomers and the development of molecules with more targeted analgesic effects and fewer psychomimetic side effects. Nevertheless, all healthcare providers involved in the treatment of acute, chronic, neuropathic, or neoplastic pain need to be aware of this treatment option and be able to manage its unique side effects.

REFERENCES

THE ROLE OF TRPA1 IN SURGERY-INDUCED SENSITIZATION OF MUSCLE NOCICEPTORS
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10.1136/rapm-2023-ESRA.670

The Nobel Prize in Physiology or Medicine 2021, awarded for the discoveries related to receptors for temperature and touch, is notably significant in recent scientific discourse. Among the receptors central to these findings is the Transient Receptor Potential Ankyrin 1 (TRPA1), a member of the TRP family channel. This channel is highly expressed in pain-sensing neurons found in the dorsal root ganglion and trigeminal ganglia.

TRPA1 is activated by a wide range of compounds, including natural substances like mustard oil and cinnamon. Additionally, it also responds to a myriad of endogenous products originating from oxidative stress and metabolism-derived substances. One such reactive oxygen species, hydrogen peroxide (H2O2), is known to stimulate TRPA1. Given that H2O2 appears rapidly at wound sites, it is suggested to play a role in wound or injury tissues.

Thus, we hypothesize that TRPA1 has a crucial role in the pain mechanism following an incision in the deep muscle tissue. Our previous research demonstrated that incised deep muscle tissue, rather than skin, primarily contributes to the genesis of non-evoked pain behavior after plantar incision in rats. We further established that TRPA1 ligands such as H2O2 are produced in wounds, and that injection of H2O2 into muscle, as opposed to skin, elicits significant nociceptive behavior through TRPA1. These findings underscore the potential contribution of TRPA1 to nociception caused by deep tissue incision.

In our recent work, we conducted several experiments and published multiple papers elucidating the role of TRPA1 in surgery-induced sensitization of muscle nociceptors. In the meeting, I am going to discuss the role of TRPA1 after surgery in deep muscle tissues, drawing on both our published and yet-to-be-published data.

DIABETIC PERIPHERAL NEUROPATHY AND INTERVENTIONAL PROCEDURES
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10.1136/rapm-2023-ESRA.671

Almost half of people diagnosed with diabetes mellitus (DM) develop diabetic neuropathy, a condition significantly impacting the quality of daily life. Such patients are estimated to require surgery at least twice as often as nondiabetic patients and are predestined to undergo several procedures under regional anesthesia.

Among several types of diabetic neuropathy, painful diabetic neuropathy (PDN) is one of the most common complications, affecting approximately 30-40% of the diabetic population. The most common presentation of diabetic peripheral neuropathy (DPN) is a distal symmetrical polyneuropathy with numbness in the distal extremities, like a stocking distribution. Common PDN symptoms manifest tingling, burning, sharp, shooting, and lancinating pain typically in feet, and as the disease progresses, it can include the entire legs and upper extremities. Such PDN symptoms often worsen at night, causing sleep disturbances, and may be accompanied by allodynia. Moreover, loss of sensation in patients with DPN can lead to unattended wounds that, combined with peripheral vascular disease and impaired wound healing, may lead to infection and, ultimately, amputation. The pathophysiologic mechanisms underlying DPN are complicated; DM leads to several pathological changes in neuronal, immune, and vascular cells that can lead to structural and functional alterations of the nervous system (e.g., inflammation, oxidative stress, and mitochondrial dysfunction), which results in DPN.
Regional Anesthesia in Diabetic Peripheral Neuropathy: Perspective of Anesthesiologists in an Operating Room

The development of DPN impacts the performance of regional anesthesia. Like other neuropathic pain conditions, such as postherpetic neuralgia, diabetic neuropathic nerves are more difficult to stimulate. The threshold of nerve stimulation has been markedly increased in DPN, and double guidance (usually ultrasonography and nerve stimulation) is safer when advancing needles. Notably, there is high inter-patient variability in stimulation threshold in such patients, and the precise value cannot be predicted accurately from detailed neurological testing (i.e., nerve conduction velocity).

According to the postulated pathophysiologic mechanisms, it is suspected that neuropathic nerves would be more sensitive to local anesthetics; therefore, lower doses of local anesthetics would be necessary for patients with DPN. Although the onset time of nerve blocks is not significantly different between diabetics and nondiabetics, DPN increases block duration. Theoretically, the decrease in nerve blood flow (deficient microcirculation) would lead to a prolonged washout phase, which was supported by Sertoz et al., that the regression time of motor block and sensory block during sciatic nerve block was significantly longer in the group with the higher HbA1C. The reasons for the prolonged block duration have yet to be clarified. However, both pharmacodynamic (more sensitive sodium currents) and pharmacokinetics (prolonged residence time of local anesthetics around the nerve due to decreased nerve blood flow) mechanisms have been suggested.

Regarding complications of nerve blocks in DPN, DM increases the risk of infection, mainly when catheters are used. Besides, a recent study by Lee CS et al. described that complicated DM increased the prevalence of deep spinal infection after epidural injections (in outpatient pain practice) three times more (odds ratio = 3.18; 95% CI = 1.30–6.7). However, despite evidence that diabetic nerves seem more sensitive to local anesthetics, there are no clinical data to suggest the regional anesthesia should be withheld from patients in whom the onset time of nerve blocks is not significantly different between diabetics and nondiabetics, DPN increases block duration. Theoretically, the decrease in nerve blood flow (deficient microcirculation) would lead to a prolonged washout phase, which was supported by Sertoz et al., that the regression time of motor block and sensory block during sciatic nerve block was significantly longer in the group with the higher HbA1C. The reasons for the prolonged block duration have yet to be clarified. However, both pharmacodynamic (more sensitive sodium currents) and pharmacokinetics (prolonged residence time of local anesthetics around the nerve due to decreased nerve blood flow) mechanisms have been suggested.

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