postoperative pain control. Traditional methods, such as opioid-based IVPCA or epidural analgesia, may offer greater pain management, but do not target various pain pathways with medications with various modes of action. Multimodal analgesia creates synergistic effects and enables the use of lower doses, minimizing side effects. Each patient should receive a customized regimen of analgesic drugs, considering things like previous analgesic use, co-morbidities, drug interactions, and tolerance. The problem of opioid abuse and associated harm must be addressed. One of the main causes of opioid misuse is the over-prescription of opioids for pain relief following surgery. To effectively prevent the opioid epidemic, actions like enhancing perioperative prescribing procedures and lowering opioid use during and after discharge are required. The restrictions on daily opioid prescriptions, the need for continuing medical education for doctors who write restricted substance prescriptions, and the facilitation of pharmacist-prescriber communication regarding high morphine doses are some of the measures that have been put into place. It is essential to understand that evaluation, customized pain management plans, and a focus on multimodal analgesia are necessary for efficient pain management following surgery. It is of utmost importance that effective pain management following surgery requires careful assessment, individualized plans, and a focus on multimodal analgesia. It is essential to consider the patient's particular experience of pain and use tested assessment techniques when self-reporting is not an option. To improve patient outcomes and reduce harm, it is also crucial to halt chronic postoperative pain and deal with the potential opioid misuse.

Conclusion For the sake of improving patient outcomes and lowering the likelihood that chronic pain may develop, closing the gaps in postoperative pain treatment presents considerable obstacles and calls for careful attention. After surgery, inadequate pain management can result in patient misery, opiate abuse, and other problems. These gaps are largely caused by several important variables, such as the misuse of opioid analgesics, the underutilization of multimodal analgesic regimens, and variances in pain evaluation and management techniques.

Future views should concentrate on applying evidence-based recommendations for postoperative pain management to address these issues. This involves using carefully crafted multimodal analgesic regimens, which combine medications that can act on both the peripheral and central nervous systems. Medications including acetaminophen, cyclo-oxygenase 2 (COX-2) inhibitors, gabapentin, and glucocorticoids may be used in such regimens. Long-acting local anesthetics injections can help people manage their pain more successfully.

To ensure consistency and top-notch care, standardized postoperative pain management quality measures should be created and put into practice. These metrics can serve as a guide for best practices and assist medical professionals in evaluating and enhancing their pain management techniques. For efficient pain management, it is essential to emphasize the regular use of approved pain assessment tools. A multidisciplinary strategy involving medical staff, decision-makers, and patients is needed to address gaps in postoperative pain management. Programs for education and training should be put in place to improve the expertise of healthcare providers in pain management. Additionally, patient involvement and education in pain management decisions can enhance results and guarantee individualized care.

#36946 KETAMINE IN ACUTE AND CHRONIC PAIN

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Acute and chronic pain remains a significant health problem worldwide. The aging of the population has led to an increased number of individuals experiencing both acute injuries and chronic diseases that cause pain. Ketamine was originally developed by Craig Newlands and later synthesized by Calvin Stevens in 1962. It is a derivative of phenylcyclidine in order to produce a safer and more manageable drug. Recently there has been an increased interest about it especially in emergency medicine, acute and chronic pain and psychiatry. It is an analgesic imperative to maintain a balance between the adequate treatment of pain and preventing opiate dependence in the population.

It is a 'dissociative anesthetic,' which refers to the fact that simultaneously different areas of the brain are either activated, such as the hippocampus and frontal cortex, or suppressed, such as the thalamus, and therefore the various areas of the brain are 'dissociated' from each other. It rapidly induces general anesthesia while preserving the patient's protective reflexes and vital functions besides its sympathomimetic effect. However, its psychomimetic effects have limited its use. Research in 1965 demonstrated its analgesic effect in subdissociative doses during painful procedures in children. In 1971, the analgesic effect of ketamine was further confirmed when it was observed that patients who underwent anesthesia with ketamine required less opioid medication and experienced better pain management.

It is highy lipophilic with a distribution half-life of 10 min, onset time of 30 s, short duration of action after a bolus dose, large volume of distribution (160-550 litres) and it is least protein bound(10-50%). The liver metabolizes ketamine via the cytochromes CYP 2B6 and CYP3A4, producing (R, S)-norketamine, which is converted to 6-hydroxynorketamine and 5,6- dehydronorketamine. These metabolites have an extended half-life of up to 3 days and, according to various authors, provide prolonged analgesic and antidepressant effects. Bioavailability and duration of action vary depending on the route of administration: with intravenous administration, bioavailability is 100%. It is eliminated mainly in the urine (elimination half-life of 1,5-3 h) Women generally metabolize ketamine more rapidly (up to 20%) than men, whereas older people tend to metabolize it more slowly. It is contraindicated during pregnancy and lactation. Due to its short half-life, no dosage adjustment is required in patients with impaired renal function.

It has the ability to produce different effects depending on the dosage and this property is unique among drugs. Low-dose ketamine has been shown to have an opioid-sparing effect and has been shown to reduce opioid tolerance. In addition to its role as an analgesic in acute pain, it can reduce hyperalgesia and allodynia in chronic pain.

The main mechanism of action of ketamine is to block glutamatergic neurons via its antagonistic effect on NMDA receptors. It does this by non-competitively blocking the opening of glutamatergic channels, mainly in the prefrontal cortex and hippocampus. Ketamine also activates the prefrontal cortex via blockade of inhibitory interneurons, which is one of the

mechanisms responsible for its psychomimetic effects. The effect of ketamine on NMDA receptors is unique in that it acts as an open-channel blocker. It blocks the calcium channels only when they are open and has no effect on the closed resting channel.

However, the analgesic effects of ketamine are diverse and multifaceted. It modulates the reuptake of serotonin, dopamine and norepinephrine and causes a paradoxical increase in glutamate with stimulation of the descending inhibitory pathways with effects on dopaminergic, adrenergic, serotoninergic, opioid and cholinergic receptors by stimulating the nicotinic pathway and inhibiting the muscarinic pathway by blocking M1 receptors. Ketamine also acts on spinal GABA interneurons.

The blockade of NMDA receptors by ketamine is involved in reducing spinal cord exhaustion, which is a major contributor to the development of chronic pain. Severe pain activates NMDA receptors with hyperexcitability of spinal interneurons in the posterior horn, leading to spinal cord wind-up and central sensitisation. The paradoxical increase in glutamate is essential for the stimulation of medullary GABA inhibitors and for the stimulation of AMPA receptors, which are crucial for the control of depressive symptoms. Ketamine blocks the NMDA-Rs of GABAergic interneurons, leading to a paradoxical increase in extra- cellular glutamate and activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAr), which stimulates the mammalian target of rapamycin complex-1 (mTORC1) signalling pathway, particularly in cortical excitatory pyramidal neurons. Ketamine also has an anti-inflammatory effect by lowering the levels of IL-6 and TNF-alpha.

In the past, great importance was placed on the analgesic role of ketamine metabolites, but this has since been revised. However, experimental evidence in animal models suggests that norketamine plays an essential role in hyperpolarizing the Hyperpolarization-activated cyclic nucleotide-gated channels (HCN) in the spinal cord and hippocampus, which is particularly important for antidepressant modulation by ketamine. However, in animal models, HCN receptors appear to be involved in the analgesic effect. The action of ketamine on opioid receptors does not appear to have a direct analgesic effect but does have a modulatory effect. Direct intrathecal antagonism of mu and delta receptors (but not kappa receptors) blocks the analgesic effect of ketamine, which is not affected by the parenteral administration of naloxone. It acts on sigma-1 receptors, L-type voltage-gated calcium channels, and voltage-gated sodium channels, but their exact functions and possible roles in analgesia are not yet known.

Concerning chronic pain there is an interesting link between pain and depression: functional and neuroimaging studies have shown that ketamine reduces the activity of the insular cortex and thalamus, which are normally activated by pain. Although the effect of ketamine on NMDA-R receptors has not been fully elucidated, some observations have suggested that these receptors play a crucial role in the context of depression and chronic pain. Specifically, ketamine increases neuronal calcium via NMDA-R blockade, which causes a secondary decrease in NMDA-R receptors via gene depression, thereby increasing levels of brain- derived neurotrophic factor (BDNF), which are low in mouse models of induced depression and whose levels are increased by ketamine. In addition, ketamine has been shown to decrease receptor affinity for substance P, a neurotransmitter that increases in chronic pain and is one of the mechanisms underlying the loss of medullary pain inhibition. In addition, ketamine appears to block acetylcholine muscarinic receptors (m1ChRs), which may also play a role in modulating chronic pain. Studies suggest that agonists of these receptors may increase the pain threshold. In addition, animal studies have suggested that ketamine may modulate astrocytic and glial responses that also play a role in chronic neuropathic pain.

It appears to have a stronger analgesic effect in patients with chronic pain and depression because it may interfere with the production of D-serine or glycine which are required by NMDA receptors in the medullary interneurons as co-agonists, especially in neurons in the limbic region involved in the development of depression and chronic pain. D-serine in medullary interneurons, increases during neuropathic pain, leading to the activation of NO synthase.

Ketamine interacts with central and spinal opioid receptors and NMDA-R. Opiates reduce pain perception by activating mu receptors, but they activate NMDA receptors, leading to postsynaptic hyperexcitability, central tolerance, and sensitization. Ketamine has been shown to modulate and reduce these effects. It also exerts a downstream effect by increasing opioid-induced phosphorylation of extracellular signal- regulated 1/2 kinase (ERK 1–2), so fewer opioids are required to achieve the desired therapeutic effect (opioid-sparing effect). This also helps reduce adverse events such as respiratory depression and vomiting.

Ketamine is indicated for managing acute pain in patients with severe pain that is not responsive to standard opioid analgesics. It can be used safely in head injuries as it does not increase intracranial pressure. It is particularly useful in major surgery and especially when the nervous system is involved. Due to differences in the surgical setting, procedures, timing of administration and dosages, meta-analyses are difficult to compare, and a large study with 8000 participants has not yet been completed.

In a recent systematic review, low-dose ketamine was comparable to morphine in analgesic effectiveness within 60 minutes of administration, with comparable safety profiles, when used in the emergency department.

In 2018 the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists published the following consensus guidelines for the use of ketamine in the management of acute and chronic pain:

1. When used for perioperative analgesia, ketamine bolus dose should not exceed 0.35 mg/kg, and infusion rate should not exceed 1 mg/kg/hr in non-intensive care settings. It should be avoided in patients with severe or uncontrolled cardiovascular disease, severe liver disease, increased intracranial pressure, elevated intraocular pressure, pregnancy, and underlying psychiatric disease associated with psychosis. Evidence supporting patient-controlled analgesia (PCA) with ketamine as the sole analgesic agent postoperatively is limited.
2. For chronic regional pain syndromes (CRPS), there is moderate certainty evidence supporting the use of ketamine infusions for analgesia, which has been shown to provide pain relief for up to 12 weeks. For fibromyalgia, cancer pain, ischemic pain, migraine headache, and low-back pain, there is weak or no evidence to support the use of ketamine infusion for immediate pain relief.
3. Oral ketamine is associated with high abuse potential and should be cautiously prescribed. Follow-up therapy (after intravenous ketamine infusion) with intra-nasal ketamine for

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.

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#36840 THE ROLE OF TRPA1 IN SURGERY-INDUCED SENSITIZATION OF MUSCLE NOCICEPTORS

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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 (H_2O_2), is known to stimulate TRPA1. Given that H_2O_2 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 H_2O_2 are produced in wounds, and that injection of H_2O_2 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.

#36970 DIABETIC PERIPHERAL NEUROPATHY AND INTERVENTIONAL PROCEDURES

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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.