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Ketamine: Old Drug but New Use for Neuropathic Pain

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Abstract

Neuropathic pain is a debilitating form of chronic pain that affects 6.9-10% of the population. Health-related quality-of-life is impeded by neuropathic pain, which not only includes physical impairment, but the mental wellbeing of the patient is also hindered. A reduction in both physical and mental wellbeing bares economic costs that need to be accounted for. A variety of medications are in use for the treatment of neuropathic pain, such as calcium channel α2δ agonists, serotonin/noradrenaline reuptake inhibitors and tricyclic antidepressants. However, recent studies have indicated a lack of efficacy regarding the aforementioned medication. There is increasing clinical and pre-clinical evidence that can point to the use of ketamine, an "old" anaesthetic, in the management of neuropathic pain. Conversely, to see ketamine being used in neuropathic pain, there needs to be more conclusive evidence exploring the long-term effects of sub-anesthetic ketamine.

Keywords

Ketamine, Neuropathic pain (NP), Clinical, Pre-clinical, Treatment

Introduction

The International Association for the Study of Pain (IASP) introduced a new definition for neuropathic pain (NP) in 2011, in which NP was and is described as "pain caused by a lesion or disease of the somato sensory system" [1]. The cause for a dysfunctional somatosensory system, and consequentially NP, can be classified into either an anatomical or etiological source. Furthermore, the symptoms associated with NP are separated into either spontaneous pain or stimulus-evoked pain [2]. Spontaneous pain is a common form of abnormal pain that occurs independently from any stimuli, and is composed of three components: paresthesia, paroxysmal, and superficial. Conversely, stimulus-evoked pain requires an external stimuli to induce a pain sensation, and is further categorized into the type of response that a patient elicits: either positive-symptoms or negative-symptoms. Positive-symptoms are comprised of allodynia and hyperalgesia, which are reflective of disproportionate neuronal activity and hyperexcitability. Allodynia can be triggered by a usually non-painful stimulus, whereas hyperalgesia is an increased pain response when evoked by nociceptive stimuli.

NP pain is usually debilitating, and due to its chronic and distressing nature it also has a negative impact on the patient's health-related quality-of-life (HRQoL). A review analysing 52 studies in patients with 6 different disease-causing NP determined that NP was associated with greater impairments in a number of HRQoL domains. The extent of impact is also dependent on the different measures of HRQoL that were utilized in each study, considering that each measure may have a different sensitivity to the effects of NP [3]. Overall, NP is associated with higher pain severity and greater interference on daily activities [3-11]. NP has economic consequences, in the form of direct NP pain costs and indirectly through impairment on quality of life, which encompasses restricted employability. In the UK, patients with post-herpetic neuralgia (PNH) and who were also attending a tertiary referral center had a lifetime cost of £770. Comparatively, a 1-year incidence cohort would differ between an overall lifetime cost of £4.8 million (incidence of 21,000 people) to £17.9 million (incidence of 78,200 people) [12].

Tricyclic antidepressants, calcium channel α2δ agonists and serotonin/noradrenaline reuptake inhibitors are the first-line treatment for NP. Unfortunately, treatment for NP pain has been inconsistent, whereby inadequate targeting of the underlying mechanism behind NP has resulted in poor pain relief in two-thirds of patients [13,14]. There is increasing pre-clinical and clinical evidence to indicate the efficacy of sub-anesthetic doses of ketamine in NP, although ketamine has been used with caution and subsequent preclusion from clinical application due to its psychotomimetic effects [15]. The intention of this review is to analyze the current body of animal model studies and clinical trials pertaining to ketamine, and to see if ketamine has a place in the treatment of NP.

Epidemiology

Questionnaires

For decades, the epidemiology of NP was understudied. This is because there were no real valid or reliable clinical instruments that could appropriately identify the various classifications of NP. Over time, researchers

began developing questionnaires that had good discriminative properties for the identification of NP, such as the Douleur Neuropathique en 4 Questions (DN4) questionnaire [16]. Other tools include: The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and its self-report counterpart (S-LANSS); The Neuropathic Pain Questionnaire; pain DETECT; ID Pain; Neuropathic Pain Scale; and Brief Pain Inventory [17].

Neuropathic pain in the general population

An extensive systematic review of epidemiological studies of NP in the general population was carried out between January 1966 to December 2012 [18]. Although data from specialist clinics, pain clinics, and studies focusing on population subgroups were excluded, the study categorized their results into patients with chronic pain and neuropathic characteristics and NP as associated with a specific condition. The underlying causes for NP are predominately herpes-zoster, diabetes, leprosy, cancer, infection by human immunodeficiency virus, carpal tunnel syndrome and trigeminal neuralgia. For each clinical condition, NP presents a different prevalence and incidence. For instance, the following conditions and their associated person-years (PY): post-herpetic neuralgia (3.9-42.0/100,000 PY) [19-22], trigeminal neuralgia (12.6-28.9/100,000 PY) [19,21,22], pain diabetic peripheral neuropathy (15.3-72.3/100,000 PY) [19,21,22] and glossopharyngeal neuralgia (0.2-0.4/100,000 PY) [22,23]. The use of rates per person-years throughout these studies is not clinically useful, as the PY is not a productive indicator of how many cases are to occur in a particular time or population. Interestingly, prevalence estimates of specific causes of NP are usually lower (1-2%) than reports on classic symptoms (6-8%) [24]. Ultimately, it has been considered that the best prevalence estimate of NP is 6.9%-10% [18]. It was also proposed that the discrepancy in prevalence of NP was due to the heterogeneity in the ascertainment tools that were used. Studies that used DN4 and S-LANSS had wider prevalence estimation (3.3-17.9%) than tailored and validated ascertainment tools (6.9-10%).

A French study identified higher prevalence of chronic pain with neuropathic features in the middle age (50-64 years), manual professions and those living in rural areas. Furthermore, the pain was associated with the lower limbs more so than any other part of the body [16]. In Germany, researchers interviewed participants by telephone, whereby 18.4% had non-NP chronic pain and 6.5% had NP [25]. The study highlighted that patients with NP were more likely to have higher pain severity, interference in daily activities due to pain compared to non-NP patients, and higher rates of co-morbidities including major depressive disorder. In the UK, patients at six family practices in Aberdeen, Leeds, and London were deemed to have a NP prevalence of 8%. Patients with NP tend to be female, slightly older, no longer married, had reduced socioeconomic levels, and the pain was more severe and longer in duration than non-NP pain [26]. In Austria, the prevalence of NP was 3.3%, with prevalence increasing to 26% in 41-50 year-olds, and 24% in 51-60 year-olds [8]. Higher rates of prevalence of NP were found in Canadian participants, in which 17.9% had NP symptoms. Once again, features of being female, economically disadvantaged, a more severe form of pain compared to non-NP, and restrictions of daily activities were reported [27].

Molecular Mechanisms of Neuropathic Pain

Multiple pathophysiological mechanisms underpin NP. Moving away from an etiology-focus to a mechanism-based approach may prove to be clinically important for improving the efficacy of the treatment options that could be available.

Peripheral sensitization

As a consequence of nerve damage, ongoing spontaneous activity and excessive electrophysiological excitability occur in the following sites: cell body of the damaged neuron in the dorsal root ganglia; the neuroma; and finally, the neighbouring functioning afferents. In other words, nociceptive primary afferents become hyperactive because of nerve damage, which is defined as peripheral sensitization [28,29].

Voltage-gated sodium channels Nav1.3, Nav1.7, Nav1.8, and Nav1.9 undergo differential expression due to nerve damage [30]. Marked changes to the voltage-gated sodium channels result in lower thresholds and an increased rate of firing [31]. Studies investigating the two inherited-pain syndromes, inherited erythromelalgia and paroxysmal extreme pain disorder, have reported gain-of-function mutations in the gene responsible for Nav1.7, *SCN9A*. Conversely, insensitivity to pain occurs when there is a loss-of-function in these sodium channels [32]. Potassium channels are also believed to play a part in NP, since peripheral nerve injury is believed to cause a reduction in potassium channel expression [33].

An inflammatory response, consisting of cytokines-IL-1β, IL-6, and tumour necrosis factor (TNF) are believed to participate in peripheral sensitization [34-37]. IL-1β is considered to exert its NP effects through a signaling cascade and secondary production of prostaglandins, bradykinin or nitric oxide. In addition, IL-1β can act directly on sensory neurons, increasing its sensitivity through a IL-1R1/TyrK/PKC mechanism [34,38]. The complex IL-6/sIL-6R, which is composed of IL-6 and its soluble receptor form, sIL-6R, promotes increased sensitivity for noxious heat through a gp130/Jak/PKC mechanism [34,38]. Finally, TNF-stimulation of TNF-receptor 1 and TNF-receptor 2 is associated with an activation of

calcium mobilization and protein kinases in neurones [38,39].

Transient receptor potential channels (TRP) are a family of channels that are expressed on sensory nerves, whereby they respond to stimuli differently. Spinal nerve injury had resulted in greater levels of TRP-ML3 in the undamaged dorsal root ganglion in comparison to the control [40]. Gene transcription is modulated through a cAMP-dependent PKA and Ca^{2+}/phospholipid-dependent PKC complex signalling mechanism, as nerve damage can disrupt the flow of signal substances from the nerves to the dorsal root ganglion cell body [41]. There is also the promotion of proteins *ERK*, *p-38*, and *c-jun*, which cause neuronal degeneration and the preservation of pain sensation [42-44].

Central sensitization

The neurones in the dorsal horn can undergo increased sensitivity in response to peripheral nerve injury. This is characterised by increased neuronal activity, an expansion of receptive fields and a spreading of spinal hyperexcitability to other sections. The central nervous system's modulation in response to peripheral nerve damage is due to a sophisticated cascade system. The sensitized C-fibres release glutamate which act on N-methyl-D-aspartate (NMDA) receptors and neuropeptide substance P on the dorsal horn neurons. Primary dorsal horn neurons interact with second-order dorsal horn neurons, since after peripheral nerve injury these neurons express abnormal Nav1.3 [45]. Central voltage-gated N-calcium channels at presynaptic sites of primary afferents are overexpressed after peripheral nerve damage, causing increased glutamate and substance P release [46,47]. In addition, mitogen-activated protein kinase system (MAPK) is an intracellular cascade that is involved in central sensitization [48]. As central sensitization takes hold, non-painful stimuli can stimulate Aδ and Aβ mechanoreceptors, triggering a painful response. Interneurons release γ-aminobutyric acid (GABA), which inhibit dorsal horn neurons. In nerve damage, there is a loss of GABA-releasing neurons, causing a reduction in inhibition [49].

Microglia and NP

A recent published review by Zhao, et al. documented the role of microglia in the pathobiology of neuropathic pain development [50]. The underlying mechanism is the release of various mediators from injured neurons including, but not limited to, Neuregulin-1, matrix metalloproteinase (MMP)-2, MMP-9, chemokine (C-C motif) ligand 2 (CCL2) and fractalkine. These mediators decrease inhibitory interneurons whilst increasing excitatory currents and the recruitment of microglial cells. Microglia release factors and cytokines, such as interleukin IL-6, IL-1β and TNF-α, that contribute to pain facilitation.

Pharmacology of Ketamine

Chemistry

Ketamine is a phenylpiperidine analogue structurally consisting of 2(2-chlorophenyl)-2-(methylamino) cyclohexanone (C13H16ClNO). It has a molecular weight of 237.727 g/mol. As well as being freely soluble in water, it is highly lipophilic [51].

It exists as two stereoisomeric forms being Esketamine [S(+)] and Arketamine [R(-)], together known as the racemic mixture, with a pKa of 7.5 and acidic pH between 3.5-5.5 [52]. Whilst the former has a greater analgesic and anesthetic potency, with studies suggesting a two to four time increase in efficacy [53,54], the enantiomers' pharmacokinetic profiles are similar. This drug is available commercially in either the form of the racemic mixture named Ketalar or the S(+) enantiomer being Ketanest-S or S-Ketamine.

Routes of administration

Clinical consideration of the route of administration is vital in preventing extensive first-pass metabolism, resulting in sub-optimal concentration of the drug in the plasma [55]. Ketamine is traditionally administered as a bolus either intravenously or through intramuscular route [56], of which the highest percentages of bioavailability are achieved at 100% and 93% respectively.

Despite this, studies have shown that it remains effective in its analgesic capacity in treating NP by rectal, transdermal, oral, sublingual and subcutaneous routes [57]. Inhalation of nebulized ketamine has recently been shown to allow rapid assimilation of the drug without the need for invasive measures in emergencies [58,59].

Pharmacokinetics

Distribution: Ketamine displays a rapid onset of acute analgesic action in NP with an alpha half-life of 11 minutes. Its lipophilic properties allow it to readily pass the blood-brain barrier, achieving a blood-effect site equilibration half-life between 1-10 minutes [53]. After IV administration, its volume of distribution is 1-3 L/kg with a re-distribution half-life of 7-15 minutes [60,61].

In relation to the long-term therapeutic use of ketamine in NP, studies have successfully shown that the onset and offset of ketamine are slower, with patients experiencing analgesic benefits up to 50 days after treatment was stopped [62]. In a study conducted by Sigtermans, et al., patients with Complex Regional Pain Syndrome Type 1 (CRPS-1), a condition characterized by chronic pain that is resistant to conventional therapy, were treated with a personalized stepwise dosage of 20-30 mg/hour of S-Ketamine over 4.2 days [63]. It was subsequently found ketamine's half-life was 11 days. As such, it is hypothesized that ketamine triggers a desen-

sitization of NMDAR restoring nociceptive homeostasis [64]. The clinical benefit of significant pain relief persists, but is slowly abated when ketamine is completely cleared by the body.

Metabolism and elimination: Ketamine is N-demethylated by the hepatic cytochrome P450 enzymes. The main isoenzyme responsible for this reaction is CYP3A4, with minor support from CYP2B6 and CYP2C9, to produce its major metabolite: norketamine [65]. This occurs within minutes after its administration through the intravenous route. As such, studies have shown that the concentration of norketamine has been found to exceed ketamine in cases where long-term bolus infusions were given [66]. Norketamine's concentration remains elevated above ketamine, acting as a non-competitive antagonist of the NMDA receptor (NMDAR). Studies are currently underway to establish the clinical implications of norketamine in anesthesiology, with preliminary findings suggesting it perpetuates algesic effects, negatively counteracting ketamine's action [66,67]. This contrasts with Goldberg, et al. who found that norketamine contributes to ketamine's analgesic effect [68]. More studies are required to elucidate the effect of norketamine on ketamine's clinical efficacy.

Elimination occurs when norketamine is subsequently further broken down into 4-, 5- and 6-hydroxynorketamine by the hydroxylation of its cyclohexane ring [69]. It subsequently undergoes glucuronidation in the liver and cleared through the kidney and bile. Studies have shown its clearance rate is 15 ml/kg/min and eliminated in 2.5 hours [70]. Following IV administration of ketamine, 91% is excreted in urine and 1-3% in faeces.

Mechanism of action

Ketamine is an uncompetitive antagonist of the ionotropic glutamatergic NMDAR receptor. This excitatory receptor is ubiquitously distributed in the brain and spinal cord, with those located in the dorsal horn of the spinal cord critically involved in nociception and allodynia [70,71]. Studies are increasingly implicating NMDAR in the induction and maintenance of central and peripheral sensitization to NP, known as the wind-up phenomena [72-74].

Ketamine exerts its strong analgesic action in NP through an extensive number of mechanisms, mainly through inhibition of NMDAR and reducing calcium-mediated neuronal death. Acutely, this prevents the afferent transmission of nociceptive signals [75]. In the long term, therapeutic administration of ketamine is believed to abate the up-regulation of the NMDAR in the dorsal horn of the spinal cord, therefore reducing the hypersensitivity of these nerves and pain perception [76,77]. As such, restoration of nociceptive homeostasis is achieved. In addition to this mechanism, Swartjes, et al. showed that ketamine stimulates the innate repair receptor (IRR) that is crucial for tissue repair and anti-inflammation in nerve damage [78]. Lastly, ketamine activates descending inhibitory, 'top-down', pathways to induce analgesia.

In addition to NMDAR, ketamine acts as an agonist to a series of receptors with the opioid receptor being the most relevant to NP. Stimulation of this receptor with the over-consumption of opioids leads to hyperalgesia, through common intracellular pathways shared with NP development [79,80]. Opioid-induced hyperalgesia is a paradoxical phenomenon in that increasing doses increases pain perception, which is mediated by opioids' pharmacokinetic profile as an NDMA agonist [81-83]. Therapeutically, numerous studies have shown that this can be counter-acted by the pharmacological inhibition of the NMDAR, with ketamine proving the most effective. Low-dose ketamine as an adjuvant significantly reduces pain scores, as well as the consumption of opioids [84,85], compared to when given opioids are administered alone [86-88].

Considerations: safety, tolerability and dosages

Ketamine use is associated with a vast array of side effects affecting mainly the cardiovascular, hepatic and nervous system [70]. A retrospective 5-year study conducted by Marchetti, et al. found that half of the patients with NP experienced side effects, with eight out of the fifty-five patients having to stop treatment [89]. It is vital comprehensive histories are taken from patients to screen out those who may be at a heightened risk of experiencing side effects.

Ketamine predominately affects the CNS, impacting both psychological and neurological functions. The most concerning of which are psychedelic symptoms occurring at an incidence of 5-30%, with recent research showing it activates reward regions in the brain including the hippocampus [90]. Liu, et al. have further implicated the dopamine system in ketamine's stimulatory effects, achieved through the cortex-striatum circuitry [91].

Neurobehavioural changes become apparent in patients, where they exhibit a myriad of sensations including but not limited to hallucinations, psychosis, anxiety, paranoia, schizophrenia-like state and frank delirium [92-94]. They may also experience intense euphoria, dissociation and depersonalization affecting their perception of visual, auditory and pain stimuli [95], as well as the essence of time [96]. Consequently, ketamine is a target for recreational abuse [97]. This stimulant effect is particularly achieved at low-doses, posing concerns for patients receiving subanesthetic doses for NP. However, in clinical practice this hallucinogenic and hypnotic effect can be attenuated with the use of benzodiazepines as co-adjuvants.

Cognitive deficits are an area of concern in the long-term administration of ketamine [98], with various

studies indicating it negatively modulates genomic expression in the hippocampus. Mouse studies by Ding, et al. [99] found that GluA1, p-S845 and p-S831 expression necessary for the functional integrity of AMPA receptors in the hippocampus are compromised. This manifested in learning and memory deficits that were largely time and dose-dependent. Morgan, et al. further supports this notion, where frequent Ketamine users, out of a cohort size of 150, had reduced performances in spatial working memory and pattern recognition [100]. They found the frequency of usage positively correlates with a higher incidence of dissociative and delusional symptoms.

In addition to this, ketamine increases cerebral metabolism, cerebral blood flow (CBF), and intracranial pressure (ICP). Administration is thus contraindicated in patients who have or are at risk of intracranial pressure as ketamine may inadvertently increase this [101].

As a sympathomimetic, ketamine stimulates the cardiovascular system through the release of catecholamines whilst acting as a negative inotrope. This presents a significant problem in clinics as myocardial depression can occur either through high doses, or through prolonged durations of infusion. This particularly affects those with a history of cardiac disease, as when administered acutely, ketamine triggers tachycardia, increased blood pressure both systemically and pulmonary, as well as induces increased myocardial oxygen consumption [102]. Screening of patients and their monitoring is thus essential in ensuring safe administration of ketamine.

The hepatic system is affected to a lesser degree with patients exposed to repetitive or prolonged infusions of low-dose ketamine exhibiting elevated liver enzyme profiles [70,102-104]. A study conducted by Noppers, et al., where patients with CRPS-1 were treated with 100 hours of subanesthetic doses of ketamine, found an elevation that was extremely profound, terminating the study out of concerns for patient safety [102]. Liver biopsies have shown changes that are indicative of liver obstruction or sclerosing cholangitis, whilst biliary imaging demonstrated dilatation of intra- and extrahepatic bile ducts. However, discontinuation of ketamine is normally followed by slow improvement, with some research indicating the normalization of liver enzymes within 3 months of cessation [105]. The benefits of the restoration of nociceptive homeostasis may arguably outweigh the risk of hepatotoxicity [63], particularly as pain relief remains weeks after ketamine treatment is stopped. As such, it is imperative that regular liver function tests are performed for monitoring to prevent the development of hepatotoxicity.

Lastly, it is important that considerations into ketamine's safety and tolerability are explored in relation to dosage regimens as studies have shown pain relief is wholly dose-dependent. In NP, Ketamine is administered in sub-anesthetic doses. Whilst there is no clear consensus on optimal dose regimens, certain studies have attempted to optimize this to specific neuropathic sub-conditions. Increased infusion durations as well as the use of adjuvants to alleviate its psychomimetic side effects also factors in ketamine's efficacy [100,106]. More studies are needed to elucidate the long-term implications of its administration in subanesthetic doses.

On the whole, ketamine is generally well tolerated and safe in clinical settings. The most common side effects are minor, including but not limited to - nausea, vomiting and vertigo. The co-administration of adjuvants, such as benzodiazepines, counteracts and alleviates its side effect profile. The majority of studies conducted on NP found that most patients found the side effects acceptable due to its efficacy in providing pain relief [63,107]. Close monitoring of the CNS, cardiovascular and hepatic systems are essential to maintain safe clinical practice.

Pre-clinical Evidence

Whilst the precise mechanism by which ketamine elicits its analgesic effects against NP remains to be elucidated, it is thought to be via its inhibitory effects on the NMDAR, which is considered a well-known target for the treatment of NP [28,72,108-112]. Ketamine has been shown to inhibit NMDAR-mediated nociceptive transmission in the thalamus [113] and spinal cord [114], as well as attenuating the frequency-dependent increase in spinal cord neuron excitability induced by the stimulation of C-fiber primary afferent neurons [114,115]. Due to ketamine's ability to attenuate the onslaught of nociceptive input from the spinal cord to the brain, in addition to its enhancement of descending inhibition and anti-inflammatory effects [116,117], ketamine is considered a potential alternative to traditional treatments of chronic pain syndromes ketamine produces [63,72]. Animal studies have consistently demonstrated the critical role that NMDAR activation has in nerve injury models, as well as the modifications of these changes when pre-empted by NMDA antagonist administration [118,119]. However, it is important to note that a recent meta-analysis of therapeutic agents in the management of NP did not find significant evidence in favour of the use of ketamine or other NMDA antagonists [13].

In addition to its effects on the NMDAR, ketamine's analgesic effects are also dependent on various other receptor systems, including monoaminergic [120], opioidergic [121], muscarinic and dopaminergic pathways, as well as microglial calcium-activated K+ channels, toll-like receptor 3 [122], and other purinergic, cholinergic and adenosine systems [76,123]. Studies investigating the effects of ketamine in mice lacking the μ-opioid re-

ceptor have demonstrated that ketamine's analgesic effects are, at least in part, mediated via the opioidergic system [124].

Pre-clinical research investigating the role of ketamine in the management of NP is both limited and inconsistent. The clinical use of NMDAR inhibitors has classically been limited by a variety of side-effects related to the suppression of physiological functions mediated by the receptors. NP is etiologically heterogeneous and various maladaptive responses within the nociceptive pathway are responsible for its development, namely changes in gene expression, alterations in gene regulation within the central nervous system, adaptations to ion channel permeability resulting in ectopic activity, and central amplification secondary to synaptic facilitation of the neural axis. As a result of the varying aetiologies and mechanisms involved in the development of NP, its treatment has been classically considered, to varying degrees, ineffective, with NP syndromes characteristically displaying resistance to standard pharmacologic therapies, including tricyclic antidepressants, GABA-ergic agents, serotonin/norepinephrine reuptake inhibitors, and calcium channel agonists [125].

Pre-clinical studies investigating NP have demonstrated that local production of erythropoietin, mediated by the receptor-ß-common receptor complex [126], following peripheral nerve injury acts to limit neuronal damage and improve nerve function [127,128]. The expression of receptor-ß-common receptor complex, termed the innate repair receptor (IRR), has been shown to be induced following inflammation and tissue injury, resulting in the transduction of specific cellular responses involving endothelial nitric oxide synthase [129], for instance, and the subsequent local production of erythropoietin [130]. Animal models investigating the effects of erythropoietin on NP have found that administration of exogenous erythropoietin is associated with an attenuation in neuronal apoptosis and pro-inflammatory cytokine production, and a restoration in anti-inflammatory cytokine production, which phenotypically manifests as reduced allodynia and hyperalgesia [131]. The novel 11-amino acid peptide erythropoietin derivative, ARA290, has demonstrated similar analgesic effects against NP as ketamine, as well as similar effects on key markers of NP, including a reduction in the expression of mRNA of the NMDAR, astrocytes, microglia and chemokine ligand 2 [78]. An animal study conducted by Swartjes, et al. (2013) investigated whether ketamine and ARA290 shared a common pathway involving the IRR to induce analgesia [78]. The study found that ketamine produced profound antinociception, however,this occurred in conjunction with significant psychomotor side effects, and with both its analgesic and side effects occurring independently of an intact IRR. This study demonstrates that, whilst ketamine has the ability to induce significant antinociception, it concurrently results in unwanted side effects, with various clinical studies indicating that these can vary from psychotomimetic effects to arrhythmias, nausea and vomiting, hallucinations and visual impairment [54,63,105,132-138].

It is important to consider the use of ketamine in conjunction with other analgesics to elicit optimum analgesic effects. The most effective management of chronic pain is by a multimodal approach and, in the setting of mixed nociceptive/NP such as cancer pain, ketamine is often co-administered with opioid analgesics. Animal studies indicate that NMDAR inhibitors, such as ketamine, act to prevent the development of opioid-induced hyperalgesia [139-141]. The term opioid-induced hyperalgesia refers to the paradoxical state of nociceptive sensitization caused by the exposure to opioids, whereby an individual's pain perception may be heightened due to acute or chronic opioid treatment, resulting in difficult ongoing pain management. The ability of ketamine to potentially reduce the incidence of opioid side-effects indicates that the combination of ketamine and opioid may be effective in the management of mixed nociceptive/NP states, such as chronic cancer pain.

Clinical Evidence

Ketamine is mainly used as a dissociative anesthetic due its ability to preserve respiratory drive. However, there is mounting evidence in support of ketamine's use as an analgesic in NP ranging from small case studies to large randomized controlled clinical trials [77].

To date, four randomized controlled, double blind trials have examined the analgesic effect of long-term IV infusion of ketamine in NP. The most recent of which was conducted by Rigo, et al. who sought to establish the efficacy of both morphine and ketamine in NP [142]. Patients with NP refractory to conventional pain management models were split into three groups receiving; IV ketamine infusions only (n = 14), methadone only (n = 14) or methadone plus ketamine (n = 14). Pain scores were evaluated using a visual analogical scale (VAS) examining allodynia, burning and shooting pain. Whilst all treatment groups were found to be effective in reducing pain scores by at least 40%, the group receiving ketamine only achieved significantly higher improvements in pain relief. No differences were observed in reducing burning or shooting pain in any treatment groups, however, ketamine showed efficacy in reducing allodynia. This study concluded that subanesthetic ketamine is effective as a sole agent in NP management.

Amr examined the effect of ketamine on patients with a history of NP secondary to spinal cord injury, utilizing a multiple day subanesthetic infusion model [143]. Group 1 (n = 20) received an 80 mg IV infusion over five hours everyday for one week with 300 mg gabapentin,

three times daily, as an adjunct. Group 2 (n = 20) were given a placebo instead of ketamine, with 300 mg gabapentin three times daily. The results showed that group 1 achieved significant reduction in pain scores during IV infusion and 2 weeks following initial treatment compared to group 2. There were no differences between the two groups thereafter. Ketamine was well tolerated and the side effects were both minimal and did not require medical intervention, where 3 out of 20 patients experienced short-lasting delusions.

Sigtermans, et al. evaluated whether S(+)-ketamine provides pain relief in CRPS-1 patients with severe chronic pain [63]. Subjects were evaluated pre-treatment, and a baseline of their pain scores were taken out of a scale of 1-10, with the mean being 7.2. Patients received either a 4.2-day IV infusion of subanesthetic ketamine (n = 30) or placebo (n = 30), where dosage was individualized to the efficacy of the analgesic effect and side effects experienced. Doses were increased in stepwise increments with a mean dose of 22.2 ± 2 mg/hr/kg. Significant pain reduction was observed in those receiving ketamine with a pain score of 2.68 ± 0.51 compared to placebo at 5.45 ± 0.48. Whilst patients on ketamine experienced nausea, vomiting and psychotropic effects, most found this acceptable. As such, one can deduce that the benefits arguably outweigh the risks.

This was followed up by Schwartzman, et al. who sought to establish the efficacy of ketamine in treating CRPS-1 with daily 4-hour IV ketamine infusions for 10 days, with a follow-up period of three months [105]. The patients were randomized into either a placebo (n = 10), where saline was substituted for ketamine, or treatment group (n = 9). All subjects received clonidine. The study showed that the treatment group demonstrated significant relief across all pain parameters that persisted 12 weeks post-treatment. The side effects experienced were mainly nausea, fatigue and headaches. Although this study was criticized by Bell and Moore [144] who argued the sample size limited the statistical significance of the results, it is clear that more studies are needed to further investigate ketamine's role in NP.

Niesters, et al. performed a meta-analysis on Schwartzman, Sigterman and Amr's randomized control trial at weeks 1 and 4 to elucidate Ketamine's efficacy in NP [70]. They found that its analgesic effect persists for at least 4 weeks, before rapidly declining suggesting that re-treatment is needed within 4-6 weeks of the initial administration. Therefore, they concluded re-admission poses financial implications.

Burst-Ketamine (BK) therapy has recently been advocated as an alternative pain management therapy. This is the infusion of subanesthetic ketamine with an opioid. Mak, et al. demonstrated a long-term anti-hyperalgesic effects persisting for 12 weeks when BK was administered, compared to 4 weeks with ketamine only [145]. An opioid-sparing effect was observed, translating into an improvement in anti-nociceptive response, which was only achieved with BK. This was the first pre-clinical study conducted on utilizing BK therapeutically in NP, and as such, further follow-up is necessary.

Topical use of ketamine has shown efficacy in achieving analgesia in various NP syndromes. This includes but is not limited to post-herpetic neuralgia, diabetic polyneuropathy and neuropathy secondary to spinal cord injuries. With NP growing in incidence in elderly patients, topical analgesia is garnering interest due to its minimal side effects and potential to be used as adjuncts to oral medication.

In a cohort size of 700 patients, Swaynok, et al. observed significant pain relief with side effects limited to application site reactions, in the administration of 4% Amitriptyline and 2% Ketamine (AmiKet) [146]. They argue that AmiKet has the potential in being first-line in treating post-herpetic neuralgia, as well as being an adjunct to oral medications to ensure both peripheral and central pain sites are targeted. Rabi, et al. conducted a smaller study on the application of topical ketamine 10% three times a day for two weeks in 5 patients with spinal cord injuries [147]. All patients reported pain relief ranging from 14-63%, with no adverse effects. Further studies with topical ketamine as an adjuvant has contributed to pain control [148]. On the whole, topical ketamine has shown efficacy in analgesia and further studies are needed.

Case studies have reported successful management of refractory NP with the use of ketamine [149,150]. Hanna, et al. managed a patient with Lichen Scleroses with a standard IV regimen, which reportedly abolished her pain syndrome completely [151]. The patient had been unresponsive to multiple pharmacological interventions, including opioids and anti-depressants. It was hypothesized that the immunomodulatory properties of ketamine was the underlying mechanism behind its therapeutic action.

In another case report, a patient with a history of Ehlers-danlos syndrome and spinal cord ischemic myelopathy presented with severe generalized body pain [152]. This was refractory to numerous pain therapies, and as such a 7-day ketamine infusion was administered reducing her pain score from 7-8 to 0-3. Secondary benefits included functional improvement in her mobility as well as a subsequent reduction in her dosage of pain medication, including opioids. Lo, et al. thus argue that ketamine could potentially reduce the chronic use of pain medication.

Conclusion

Neuropathic pain is a devastating and debilitating form of chronic pain that affects individual's physical

and psychological well-being, quality of life and functionality. Recent pre-clinical evidence exists to suggest that ketamine elicits its analgesic effects in neuropathic pain states by inhibiting NMDA-mediated signaling pathways. Pre-clinical findings also indicate that ketamine may be a useful adjunct to traditional opioid analgesics to elicit optimum analgesic regimens. However, clinical evidence is currently limited, with only a small number of randomized control trials (n = 4) indicating the efficacy of ketamine in attenuating neuropathic pain, whilst no improvement was noted in the psychological state or functionality of patients suffering from chronic neuropathic pain. Furthermore, both pre-clinical and clinical data continue to suggest that ketamine administration is associated with a variety of unwanted side-effects affecting the cardiovascular, hepatic and nervous systems, manifesting as tachycardia, systemic and pulmonary hypertension, dizziness, hallucinations, psychosis, anxiety, paranoia and a schizoid-like state. Despite evidence for ketamine's analgesic effects in neuropathic pain states, due to its extensive side-effect profile, it is likely that ketamine should be restricted to patients with treatment-resistant, refractory neuropathic pain. Ketamine has always been classically considered as a drug that requires close monitoring due to its anesthetic and sedative effects. In order for ketamine to be a viable option in the management of neuropathic pain in the outpatient setting, tailored and smart dosing regimens are necessary and frequent input from clinicians is required in order to monitor patients and avoid toxicity or abuse. Whether outpatient or at-home, ketamine monitoring would be feasible in clinical practice remains to be elucidated. Further well-powered randomized control trials are certainly warranted in order to be confident of ketamine's analgesic efficacy and to further understand its side effect profile. This is pertinent in order for clinicians to make informed decisions regarding the risks and benefits associated with its use.

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