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Ketamine in Current Clinical Practice: Anything New to Write Home About?

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Abstract

Ketamine has proven to be a potent and safe drug for over five decades. While its active enantiomer is S(+)-ketamine, the most widely distributed formulation combines S-ketamine with the weaker R(+) enantiomer. The pharmacology of the drug is well-established. Its main metabolite is not nor ketamine, which is responsible for most of its neuropharmacological activities that result mostly from the blockade of N-Methyl-D-Aspartate (NMDA) receptors; which decrease the "wind up" phenomenon and enhance the descending inhibition pathways in the spinal cord. Past-psychomimetic events were related to high-dose protocols that have now been replaced by "sub anesthetic" doses.

Introduction

Ketamine has low oral bioavailability due to its extensive first-pass hepatic metabolism. Nevertheless, recent sublingual, intranasal, intraosseous, transdermal, and rectal formulations have proven to be viable alternatives to Intravenous (IV) and Intramuscular (IM) administrations when treating both short-term and protracted pain [1,2]. Ketamine uniquely preserves cardiac output and respiration, making it an excellent drug that is suitable for hemodynamically and neurologically unstable patients, as well as those who sustained physical trauma. Recent data have enhanced ketamine's appeal for perioperative use in small children and in the elderly, providing them a new window of opportunity to be studied more extensively in Randomized Controlled Trials (RCTs). Recent findings of ketamine's neuropharmacological activities have also highlighted its value in hard-to-treat depressive patients, a subject of considerable interest in many recent publications [3,4]. This review will present findings that have been made available during the last few years.

Acute Pain

Traditional administration of ketamine was *via* Intravenous (IV) or Intramuscular (IM), and the doses were high (1.5 to 2 mg/kg and 5 mg/kg, respectively), following animal assigned weight related ratios. Following the performance of clinical investigations, the doses have significantly and progressively been reduced, reaching the current "sub-anesthetic" levels. Preoperative Intravenous (IV) boluses now range between 0.25 to 0.5 mg/kg, and they are effective in reducing both pain and opioid consumption [5,6]. When given perioperatively, the preoperative boluses are usually followed by infusions that continue to be administered until the skin is sutured [7,8]. Most intraoperative infusion doses of ketamine range between 0.1 to 0.25 to 0.3 mg/kg/h [8,9]. Postoperative Patient Controlled Analgesia (PCA) is another useful mode of acute pain control, where ketamine is either used alone or combined with opioids or other groups of drugs, usually without background infusion [7,10]. PCA ketamine protocols can incorporate intraoperative ketamine or other analgesic techniques. Non-systemic routes of ketamine administration are newer models for providing pain control, even when combined with local anesthetics. Those approaches include epidural, intrathecal, intranasal, oral, rectal, and percutaneous applications, as well as peripheral neural blocks [7,11-15]. Past observations of untoward psychosomatic effects that followed the administration of ketamine had banned it from use by some institutions that held that the drug must be administered only where resuscitative measures are available. These reservations have now been rejected following reports on the favorable results of ketamine usage even in pre-hospital settings, in emergency and combat areas, and in emergency and hospital departments, as well as among pediatric and geriatric populations that were earlier beyond consensual use and investigation of ketamine [16]. Children are a group of population who requires the most safe and adjustable drugs that provide predictable pharmacological effects and reliable and unfailing awakening process. These especially benefit from the fact that ketamine does not depress respiratory and cardiovascular parameters, which

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is especially relevant when co-administering opioids. Ketamine diminishes the latter's depressive effects since it minimizes opioid use [17]. Moreover, ketamine provides effectiveness and safe pain control even in very young children [18-21]. The Intravenous (IV) or Intramuscular (IM), associated psychomimetic events that were reported in the past are among kids are rarely seen nowadays, mainly because of the use of sub anesthetic doses and not the 6 to 8 times higher doses that had been used some 20 years ago. These updated findings taken together support the contention that ketamine is an optimal analgesic solution for both sedations and interventions in the pediatric population [18,22-24].

Elderly populations were rarely included in RCTs in the past due to their altered pharmacokinetics and dynamics compared to younger adults. These limitations restricted the availability of relevant data to clinicians. The use of ketamine has been recently extended within the geriatric population, leading to encouraging results. Recent data revealed that ketamine was not inferior to other sedatives (e.g., benzodiazepine) or analgesics (e.g., dexmedetomidine) [25]. Moreover, ketamine additively affects analgesia when combined with various analgesics [26]. These studies also confirmed ketamine's safety, with the rates of adverse effects within ranges similar to those detected within the average non geriatric population. A report of eye surgery carried out on elderly patients under ketamine sedation (0.3 mg/kg/250 ml saline after initial sedation and throughout surgery) further exemplified ketamine's safety and satisfaction by both patients and physicians [27]. Low dose ketamine protocols have also successfully improved acute pain management after total knee replacement, a frequent intervention among the elderly [28,29]. Several studies found that small-dose infusions of ketamine after other orthopedic interventions were indeed associated with less morphine consumption and more rapid attainment of rehabilitation than placebos [17,30-32]. It was also reportedly superior to other agents in controlling pain when the latter failed to achieve their goal or when used in opioid-tolerant patients [33]. One systematic review described the successful use of ketamine for preventive analgesia for bone fracture in the elderly [34-36]. Ketamine infusion rates as low as 2.5 μg/kg/min that are used by some anesthesiologists seem to be as effective as doses used by others that are 4 times higher (1 mg/kg/min) [35,37]. Interestingly, even postoperative hallucinations and delirium were reportedly effectively treated with ketamine [38].

Chronic Pain

Chronic pain is a condition that is rarely controlled to the patient's satisfaction. This is due to continuing changes in the neurohumoral activation/inhibition pathway, amplification of perioperative pain and its modification into neuropathic pain, frequent development of complex regional pain syndrome, long-term inefficient acute pain control associated or not with lack of adequate compliance of the patient with the treatment protocol, as well as to patient anxiety, work disability, and social maladjustments. In addition to non-steroidal anti-inflammatory drugs, opioids are frequently prescribed in such cases in spite of their known limited efficacy. Invasive interventions, such as epidural block, neural block, or radiofrequency treatment, are also used in such cases. All of these are often of brief effectiveness. The efficacy of ketamine in controlling secondary hyperpathy, hyperalgesia, allodynia and long-standing pain have been documented by this and other authors [11,16,39]. Its use as an adjuvant in oncological and orthopedic-oncological patients also yielded additive satisfactory analgesic effects [10,40]. Several RCTs on patients suffering from chronic back pain have been recently published. Most of those patients received an intraoperative S-ketamine bolus of 0.5 mg/kg followed by infusion 0.25 mg/kg/h or placebo. The drug-treated individuals reported lower pain scores and performed better in rehabilitation [9]. Despite the efficiency of ketamine in patients already diagnosed with chronic pain, various baseline conditions and drug treatments affect grades of responsiveness to ketamine, and ketamine's definitive dose ranges, which have not yet been established yet [41,42]. Importantly, the rates of adverse effects also depend on those dosages and the duration of ketamine's infusions [43,44]. Thus, although the pathophysiology of neuropathic pain is still not well understood, but ketamine appears to is a promising treatment for chronic neuropathic pain in the clinical setting. Further high-quality clinical evidence, such as RCTs, is needed to evaluate wide variety of pain conditions and their backgrounds, various routes of administrations, and time-diverse lengths of treatments, in order to better quantify the efficacy, refine the optimal therapeutic dose ranges in the various chronic cases, and determine the effectiveness of ketamine via various routes of administration, during long-term treatments [42].

Ketamine and Psychiatry

Psychiatry is a third field of interest in which recent investigations on ketamine have contributed considerably. Ketamine began attracting the interest of psychiatrists two decades ago in parallel with the understanding that severe, acute or chronic pain and depression are often dual phenomena of a single disorder. It was also observed that while depression remained unaffected by prescribed drugs, such as SSRI, ketamine-treated patients seemed to handle their symptoms better, as when administered parenterally [45,46]. Initial case reports and small studies cautiously tested 1-min Intravenous (IV) injection of ketamine 0.5 mg/kg in long-standing, chronically depressed mostly hospitalized patients in poor or desperate conditions [47]. The results were considered to hold promise in the treatment of depression, mainly for drug-refractory sufferers [48,49]. Later studies pointed to optimal effects of prolonged low-dose oral ketamine in cases of behavioral despair and spatial non-working memory in male Sprague-Dawley rats, among which the antidepressant effect emerged within 10 consecutive treatment days and lasted 30 days [50]. A recent multicenter, double blind, randomized, prospective, optimization and withdrawal study examined more than 700 adults with confirmed treatment-resistant depression. Of 455 patients who were treated with esketamine nasal spray (56 or 84 mg weekly or twice weekly) plus an oral antidepressant for 16 weeks, 297 individuals achieved stable response or remission, compared to placebos [51]. Similar results were obtained from an RCT that was conducted in 39 adult outpatient referral centers. Moderate-to-severe non psychotic depression and a history of non response to at least two antidepressants during a current episode, with one antidepressant assessed prospectively, were preconditions for the study. The patients received either esketamine nasal spray (56 mg or 84 mg twice weekly) and an antidepressant or an antidepressant and placebo nasal spray. Of the 435 patients that were screened, 227 underwent randomization and 197 of them completed the 28 days double blind treatment phase. The change in the Montgomery-Asberg Depression Rating Scale (MADRS score) with esketamine plus antidepressant was significantly greater than the change with antidepressant plus placebo at day 28. Clinically meaningful improvement was also observed in the former arm at earlier time points. Nevertheless, the five most common adverse events (dissociation, nausea, vertigo, dysgeusia, and dizziness) were more frequent in the former, causing 7% *vs.* 0.9% of

the respective groups to discontinue the study. The adverse events in the esketamine plus antidepressant arm generally appeared shortly after dosing and resolved within 1.5 h after it [52]. A recent review of two RCTs that assessed the antidepressant effects of oral ketamine demonstrated that antidepressant efficacy and good tolerability was associated with significant changes in depressive symptom severity was not observed until after 2 to 6 weeks of treatment compared to the immediate antidepressant effects associated with Intravenous (IV) ketamine. The antidepressant and anti-suicide effects and the pharmacological efficacy in treatment resistant depressives occurred within 24 h of treatments ranging between 0.5 to 7.0 mg/kg 3 times daily or once monthly, compared with most studies that provided dosages of 1 to 2 mg/kg every 1 to 3 days. Importantly, no clinically significant adverse effects were reported [53]. In a small randomized, double blind, placebo-controlled, proof-of-concept trial, 41 participants received either 1 mg/kg oral ketamine or placebo thrice weekly for 21 days. Evaluations were performed at baseline, 40 and 240 min post-administration, and on days 3, 7, 14, and 21. The main outcome measure was a change in the MADRS. Twenty two drug treated patients showed an immediate decrease in depressive symptoms, whereas the placebo-treated controls evidenced them only at 40 min post administration. Additionally, the MADRS score on day 21 was 12.75, which was 5 times higher in the ketamine group compared with 2.49 in the placebos. Furthermore, 6 ketamine individuals achieved full remission compared with none of the controls (the number needed to treat for remission was 3.7) [46]. A recent study on esketamine (Spravato™, prescribing information. Titusville, New Jersey, 08560: Janssen Pharmaceuticals, Inc.; 2019) analyzed the anti-depressive effects of ketamine administered intra nasally in conjunction with oral antidepressants. Both esketamine and placebo were provided *via* nasal spray devices, each containing 200 ml of solution (i.e., 2 sprays). Each device contained 32.28 mg of esketamine hydrochloride (28 mg of esketamine base) or placebo (denatonium benzoate). The MADRS at weeks 1, 2, and 4 as well as weekly observations during the induction, optimization, maintenance, and follow-up of the drug indicated ketamine's benefits [54]. A word of caution: patients using such devices must be under the direct supervision of a health care provider for monitoring physical and mental changes for several hours, and activities requiring precision, including driving, is to be avoided. It is worth noting that prolonged use of benzodiazepines, ketamine, stimulant medications, and cannabinoid, while allowing for short-lasting benefits, may promote the development of addiction to prescription medications. This raises dilemmas regarding the appropriateness of their lengthy prescription for patients with depression and anxiety disorders [55]. However, many psychiatrists contend that since repeated oral ketamine produces rapid and persistent amelioration of depressive symptoms in outpatients with TRD, and since the drug is well tolerated, add-on oral ketamine may soon become the first line drug for patients suffering from treatment-resistant depression in the community [46]. This is especially pertinent when there are limited therapeutic options in terms of efficacy, side effects and patient acceptability. Esketamine is thus expected to address an unmet medical need in this population through its unique mechanism of action and rapid onset of antidepressant efficacy. These latter claims are supported by reports such as the one showing esketamine's efficacy and safety via nasal spray as a rapidly acting antidepressant for patients with treatment-resistant depression [52]. Similarly, oral doses of ketamine, as low a dose as 0.15 mg/d/4-6 weeks, given either sublingually or transmucosally, enable severely depressed patients feel less anxious, regain optimal relationships with their surroundings, and ease from considering suicide as a real solution to their subjective agonizing state [56]. It is important to bear in mind that clinical optimization of dosage and time of treatment have not yet been established [56,57].

Conclusion

While recent publications have not revealed new fields of interest or applicability of ketamine that were unknown before, they are characterized by more in-depth explorations into three areas of interest: ketamine's role in the field of psychiatry, its benefits in chronic pain, and its safe use in small children and the elderly. These innovative testimonials generate enthusiasm among pain specialists, psychiatrists, and rheumatologists, whose armamentarium is fairly limited when encountering difficult clinical conditions in the above-mentioned settings. Ketamine thus appears to have recovered its good name and will remain therapeutic in many and varied medical fields throughout the years to come.

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