Peri-operative Ketamine for Acute Pain Management

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Key Points

1. Ketamine is useful as a co-analgesic and antihyperalgesic, thereby decreasing post-operative pain, opioid analgesic requirements and opioid related side-effects following major abdominal surgery.
2. High-dose ketamine is >1 mg/kg as bolus and >1 mg/kg/h as infusion; low-dose constitutes 0.1–1 mg/kg bolus and 0.1–1 mg/kg/h infusions and ultra-low dose is <0.1 mg/kg and <0.1 mL/kg/h infusion.
3. Post-operatively it may be added to an opioid for PCA use.
4. This will assist the patient in achieving their ERAS goals, i.e., early mobilization, early nutrition and discharge with improved satisfaction.

Introduction

Ketamine was first introduced into clinical practice over 50 years ago as a dissociative anaesthetic [1]. It has since been used for pre-medication, sedation, induction and maintenance of general anaesthesia and for post-operative analgesia. Despite this long standing and wide use both as an anaesthetic and analgesic, its peri-operative role has enjoyed a somewhat waxing and waning popularity. In pain management, ketamine's use has ranged from treating battlefield trauma and burn injuries to acute and chronic, cancer and non-cancer pain. The peri-operative use of ketamine is now backed by extensive experience and good quality evidence [2].

The peri-operative role of multimodal analgesia has been discussed in detail in the preceding chapter on intravenous lidocaine. An acute pain management framework

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based on the WHO ladder concept provides us with a step-wise, severity-based, opioid-sparing approach. This has been accepted and implemented widely in simple and standardised peri-operative protocols. The dual appreciation of the role of pronociception in acute pain and the emerging understanding of opioid-induced and opioid-resistant hyperalgesia has led to the recognition for the need for appropriate non-opioid adjuvants with anti-hyperalgesic properties (*see* Chap. 6, Fig. 6.2).

Due to the concurrent introduction of laparoscopic surgery, and the emergence of the principles of Enhanced Recovery after Surgery (ERAS) for abdominal surgery in the past two decades, the entire peri-operative paradigm has shifted from 'bigger and slower' to 'smaller and faster'. In parallel with these surgical changes, there has been a quest for a suitable alternative to epidural analgesia coupled with a renewed interest in *parenteral* non-opioid analgesia. It is in this context that ketamine (and lidocaine) can play a major role by ensuring adequate pain relief coupled with minimal immediate side effects and quantifiable long-term benefits.

Another aspect of multimodal analgesia is that despite recent advances in the pharmacotherapy of acute pain, ketamine remains the *numero uno* non-opioid anti-hyperalgesic adjuvant available for use in peri-operative pain management. Therefore, the role of ketamine in pain management after abdominal surgery cannot be ignored or underestimated [2, 3].

To incorporate ketamine into acute pain management after abdominal surgery it is therefore important to understand the pharmacology of this drug, critically evaluate the evidence for its use and appreciate the practicalities of using ketamine in a rational peri-operative pain management plan.

Pharmacology of N-Methyl-D-Aspartate (NMDA) Receptors (NMDARS)

The NMDARs belong to a class of ionotropic glutamate receptors that also includes the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs) and kainate receptors. Excitatory synaptic transmission in the vertebrate brain relies on the release of L-glutamate from presynaptic terminals that diffuses across the synaptic cleft and binds to postsynaptic AMPARs and NMDARs. Activation of AMPARs is fast and transient, causing brief depolarizations that last no longer than a few milliseconds. NMDARs are not critical for this basal synaptic transmission, but instead they regulate functional and structural plasticity of individual synapses, dendrites, and neurons by allowing activation of specific calcium (Ca^{2+}) dependent signaling cascades [4].

NMDARs are densely expressed at nociceptive synapses in the spinal cord dorsal horn. At resting membrane potentials, external magnesium (Mg^{2+}) ions enter the NMDAR pore, but unlike the permeant calcium (Ca^{2+}) ions, they bind tightly and prevent further ion permeation. A depolarization of sufficient amplitude and duration is required to dislodge and repel the Mg^{2+} ions from the pore, thereby allowing the flow of permeant Ca^{2+}ions. As a result, the NMDAR acts as a molecular coincidence detector: efficient activation and ion permeation through the NMDAR requires both a sufficiently strong depolarization and synaptic release of glutamate. This dual input

requirement, together with the slow activation and deactivation allows NMDARs to integrate and decode incoming synaptic activity. The additional high Ca^{2+} permeability of NMDARs enables them to transduce specific synaptic input patterns into long-lasting alterations in synaptic strength. Activation of the NMDAR occurring after an intense or repeated stimulus results in increases in cell excitability because of second messenger effects initiated by the calcium influx [1, 2].

This role of NMDAR in nociceptive transmission has been well established in humans. In acute nociceptive pain, the Mg^{2+} ions get pushed out into the synaptic cleft and the NMDAR opens to Ca^{2+}, which then activates the second messenger system that propagates the signal. When prolonged or repetitive signalling through the synaptic cleft occurs, the NMDAR can get involved in sustained neuronal hyperactivity i.e. simple signal propagation can change into transmission persistence despite cessation of input stimulus. Hyper-excitability of the NMDAR also explains the development and maintenance of what can be called "pathologic pain" or pronociception, i.e., increased pain perception as a result of pain sensitization and synaptic plasticity [2]. A NMDAR-mediated increase in dorsal horn synaptic efficacy is therefore thought to be an important contributor to the central sensitization of pain pathways seen in acute hyperalgesia, opioid tolerance, opioid-induced hyperalgesia (OIH) and in chronic pain syndromes [5]. Finally, while ongoing and future work may confirm that NMDAR activation is the sentinel event in the progression of acute pain to chronic pain, its pharmacology will continue to play a pivotal role in managing acute pain and hyperalgesia (Fig. 5.1).

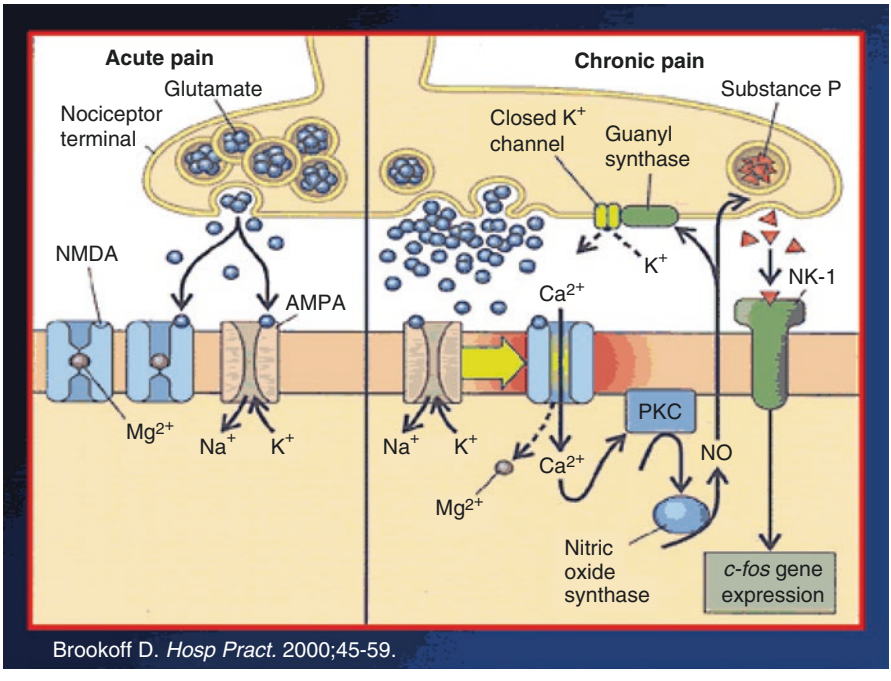

Fig. 5.1 The role of the NMDAR in acute and chronic pain. From [31]; with permission

The clinical relevance of these functions of the NMDARs in pain transmission, amplification and perpetuation is the basis for the use of its antagonists (ketamine, dextromethorphan, nitrous oxide and methadone etc.) in peri-operative pain management [1–3].

Pharmacology of Ketamine

Ketamine is the most widely used, well studied and probably the most potent NMDAR antagonist. It is a phencyclidine (PCP) derivate that was synthesized in 1963 and first used as an intravenous anaesthetic in 1965 [1]. It was approved for clinical use in 1970 and was initially used primarily as an anaesthetic in war-time, natural disasters, other remote and low resource areas. Early experience suggested that wide acceptance would be limited by the side effect profile i.e. the dissociative state during, and the psychomimetic emergence reactions after use. Nevertheless, early users documented the cardio-respiratory stability and the profound analgesia that also lasted well beyond the duration of infusion. Ketamine remains on the WHO's list of Essential Drugs. One of only two intravenous anaesthetics on this list which probably reflects its continued versatility as a relatively safe solo-agent intravenous anaesthetic.

Ketamine has been widely used for decades in veterinary surgery as an anaesthetic and has earned the moniker "horse tranquilizer". This extensive use of ketamine clinically for both human and animal use led to its increased production and subsequent widespread availability. Unfortunately, this use has indirectly also led to a significant increase in the diversion for non-clinical use and abuse of ketamine. The 'street', 'club' and 'party' use of ketamine (dubbed "Special K") is administered through a variety of routes and has unfortunately cast a shadow on its clinical use. This has led to the requirement for implementation of more stringent control measures with restricted prescribing and dispensing. These two issues, the veterinary use and the abuse, are well known to the public and at times perceived as barriers to use by both patients and other healthcare providers. We believe that it is important to discuss and disclose these issues to patients receiving ketamine for post-operative pain.

Ketamine is 2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride and consists of two enantiomers. While racaemic ketamine is more widely available the world over, the S-ketamine variant is more potent with fewer side effects and has been used extensively in Europe. Ketamine is prepared as a water and lipid soluble hydrochloride salt and is approved only for parenteral administration i.e. intravenous, intramuscular or subcutaneous. Other routes of administration for example neuraxial (spinal, epidural or caudal), enteral (oral, rectal) and others (nasal, sublingual and topical) continue to be described in off-label use [1, 2].

Ketamine has low plasma protein binding and high lipid solubility allowing for rapid uptake (alpha elimination 4–5 min), distribution and elimination (beta half-life of 2–3 h). Most (up to 80%) of the intravenously administered drug will be metabolized in the liver by cytochrome P450 system to norketamine whose potency

is approximately a third of the parent drug. Ketamine and norketamine are excreted by the kidneys and can both accumulate in renal failure. The clinical relevance of the pharmacokinetics of ketamine in hepatic and renal impairment is the decreased metabolism and delayed elimination respectively, thereby requiring dose or administration frequency reductions [1].

Ketamine primarily binds noncompetitively to the phencyclidine binding site of NMDARs and also modifies them *via* allosteric mechanisms thereby decreasing the glutamate transmission of synaptic impulses. Since these receptors are present in the thalamus and the limbic system in addition to the spinal cord, depending on the dose, the NMDAR mediated actions can have spinal and supraspinal effects. Ketamine may also have effects on dopamine, noradrenergic, serotonergic and opioid receptors. These may not be clinically relevant in the management of perioperative pain. The cardiovascular, respiratory and gastrointestinal effects of ketamine could have an impact on the pain management of some patients and these have been well described elsewhere [2, 3].

The clinical effectiveness of ketamine in pain management requires the careful determination of the optimal balance that would provide benefit (analgesia) and avoid side effects (psychomimetic and disassociation). In our experience, the patient-to-patient variability with regards to analgesia from ketamine is small. The clinical presentation i.e. the cause of pain, severity, presence of acute hyperalgesia and concurrent opioid administration may be more important for the determination of the appropriate dose for each patient. Patients presenting with acute hyperalgesia, higher pain scores and increasing opioid requirements demonstrate the greatest benefit from the administration of ketamine. If an objective diagnosis of acute neuropathic pain is required to determine the need for ketamine, the DN4 questionnaire may be effectively used.

The clinical effects of ketamine can be described depending on the dose administered. In our experience, irrespective of most patient characteristics, these effects are almost always consistently observed. The dose of ketamine used peri-operatively can be arbitrarily divided into “high”, “low” and “ultra-low”.

It is unusual to use ketamine for pain relief in ‘anaesthetic dose’ or ‘high dose’ range (>1 mg/kg IV or >1 mg/kg/h infusion). At these levels, despite the profound analgesia, the patient will have unpredictable and persistent CNS effects i.e. loss of consciousness and airway reflexes, apnoea, labile cardiovascular effects, disassociation and lasting psychomimetic effects. The most significant latter can include unpleasant dreams, nightmares, abnormal sensations, emergence agitation, delirium, hallucinations and acute psychosis. In fact, at these doses, ketamine can be used to treat ECT-resistant depression and has even been reported to produce a pharmacologically induced model of schizophrenia [1].

When administered in a sub-anaesthetic “low dose” range (0.1–1 mg/kg IV bolus or 0.1–1 mg/kg/h infusion), ketamine’s analgesic efficacy correlates well with analgesia (or anti-nociception). It is induced directly at the spinal level (inhibition of NMDAR mediated pain facilitation) and indirectly at supraspinal level by decreasing the activity of brain structures that respond to noxious stimuli. It has also been shown that ketamine is able to modulate the transmission of pain

impulses via interactions with the other receptors and pathways. Depending on the dose of ketamine, this anti-nociception may be due to the facilitated inhibition of the spinal opioid receptors or activation of the descending pain inhibitory monoaminergic pathways expressed at the spinal level by the alpha 2-adrenoceptors. Interestingly, the antinociception of ketamine at 0.3 mg/kg is not reversed by naloxone, suggesting that the opioid receptor agonistic activity was not involved in pain control [6].

"Ultra-low dose" ketamine refers to the use of less than 0.1 mg/kg bolus or less than 0.1 mg/kg/h [7]. This is probably the most useful dose of ketamine for post-operative use, especially in awake patients, as it avoids any CNS side effects. It probably works at the spinal level as a true co-analgesic adjuvant as it improves the analgesic effects of co-administered opioids. The affinity of ketamine for NMDA receptors is several-fold higher than for the non-NMDA receptors (mu and alpha receptors or the monoamine transporter sites). Therefore, at the lowest doses, it is possible that ketamine could interact almost exclusively with NMDA receptors rather than with the alpha receptor. This may explain its effective modulation of pain impulse transmission or anti-pronociception. There is some evidence from animal studies that at low dose ketamine may also directly provoke peripheral nociceptors, inducing analgesia and modulation within the peripheral nervous system. Animal studies have shown that locally administered ketamine effectively prevented withdrawal in formalin and thermal hyperalgesia testing in rats. Although ketamine exhibits promise as a potential topical analgesic in humans, the mechanistic basis of its peripheral actions is not well understood [8].

There may also be a significant synergistic interaction between opioids and NMDA antagonists. It has been postulated that ketamine can prevent central sensitization because while opioids can block the initial response of dorsal horn nociceptive neurons to C-fiber stimulation, NMDA antagonists inhibit the potentiation of abnormal and exaggerated responses on sustained or repeated stimulation [9].

There are two other important clinical situations where ketamine may also be useful. Firstly, it is well known that opioids themselves can worsen pain—*opioid-induced hyperalgesia* (OIH). Secondly, when increasing doses of opioids produce diminishing analgesic effects, clinical *opioid tolerance* is suspected. Both these paradoxical effects of opioid use are not restricted to the long term or long acting formulation use and can be seen in the early post-operative period. They are likely due to the interactions between, and activation of, the NMDARs by the mu-receptor agonists [6]. Ketamine may therefore be the drug of choice to prevent and or treat OIH and prevent the development of opioid tolerance in acute pain management [3].

Evidence for Efficacy

As mentioned earlier, clinical evidence for the use of ketamine dates back more than 4 decades [1]. The intra-operative cardio-respiratory stability was well documented in earlier studies, which also supports the safe use of this drug with minimal

monitoring after surgery [10, 11]. The profound analgesia reported was also documented to last beyond the duration of injection or infusion. This was then a poorly understood analgesic effect but nevertheless probably further encouraged its continued and wider use as an anaesthetic in a variety of remote and low-resource settings, e.g., warfare, natural disasters, humanitarian outreach programs etc. Despite the safety profile, the use of ketamine as a sole anaesthetic or analgesic agent was, and is, limited by the potential for psychomimetic side effects and emergence like phenomena. These considerations continue to limit the dose, duration and overall use of ketamine for acute post-operative pain [2, 13].

Ketamine has been shown to be useful in the reduction of acute post-operative pain and analgesic consumption in a variety of surgical interventions with variable routes of administration [12]. Interest in the analgesic properties of low-dose ketamine has prompted clinical trials comparing opioids and ketamine [13]. Others have reported that peri-operative low-dose ketamine may be useful in a variety of clinical settings [14]. They also suggested that ketamine may be given at any point (pre-emptively, intra-operatively, post-operatively) and in any method (bolus, infusion, patient-controlled analgesia co-administration), but would be most useful when the anticipated post-operative visual analog scale (VAS) score is greater than 7/10 and when the site of surgery (and possibly the extent of the incision) has an impact on the efficacy of ketamine as a peri-operative adjuvant drug. However, they postulate that pain severity is more important than surgical site and conclude that abdominal surgery patients should receive ketamine, especially those patients or procedures where significant post-operative pain is expected [14].

Although many studies have suggested that peri-operative ketamine administration could be useful to control post-operative pain, their results are often difficult to compare due to the various ketamine dose regimens used [15]. The distinction of the infusion dose as being ‘high’, ‘low’ and ‘ultra-low’ dose (see preceding section) will probably contribute in the future to an improved understanding and increased confidence leading to wider and safer peri-operative use of this drug.

The importance of an ‘adequate’ dose of ketamine has been emphasized, in order to prevent the induction of central sensitization caused by stimulation of peripheral nociception together with blocking the wind-up phenomenon [13]. Studies have reported the adequacy of using a ketamine bolus of 0.5 mg/kg IV bolus followed by a 0.12 mg/kg/h infusion [15]. This was calculated to obtain a theoretical plasma ketamine concentration in the range of 100 mcg/mL previously described as being the therapeutic plasma concentration of ketamine for analgesia. At this and lower plasma concentrations, both psychomimetic effects and accumulation are likely to be avoided [15].

The dose of ketamine may also require adjustment according to the procedure. An arbitrary distinction into ‘painful’ and ‘less painful’ procedures has also been suggested. For the former a 0.5 mg/kg slow bolus injection of ketamine before or after induction of general anesthesia, was suggested. This may be followed by a continuous infusion of 0.5 mg/kg/h. In procedures expected to be less painful, a 0.25 mg/kg ketamine bolus before incision is recommended followed by infusions of 0.25 mg/kg/h. The continuous intra-operative infusion may also be replaced by

appropriate hourly boluses. For procedures lasting longer than 2 h, these authors recommend that the infusion cease at least 60 min before surgery to prevent prolonged recovery [2].

In open abdominal surgery, continuous epidural analgesia is still probably the 'gold standard' for post-operative analgesia. Despite the use of local anaesthetics containing opioids insufficient epidural analgesia after surgery is not infrequent. This inadequacy of epidurals can be caused by epidural blockade failures, unilateral blockade, dose infusion limitations, developing relative or absolute contraindications (sepsis, anticoagulation, localized infection, delirium etc.) and/or patient intolerance to side effects (hypotension, postural symptoms, inability to ambulate etc.).

It has been suggested that combined and pre-emptive administration of ketamine with epidural analgesia may improve the quality of epidural analgesia in the post-operative period [16]. Neuraxial opioids may also result in acute tolerance to opioids and systemic ketamine may be required to prevent the development of acute tolerance to opioids. It has been postulated that viscero-peritoneal nociception is transmitted by multiple spinal nerves and the vagus nerve [17]. This nociception induces central sensitization not only segmentally, but also multi- and supra-segmentally. One of the analgesic action sites of ketamine is known to be supraspinal i.e. ketamine might block brainstem sensitization via the vagus or phrenic nerve during upper abdominal surgery. This may explain the frequently observed effect of ketamine in potentiating the epidural analgesic effects of the neuraxial opioid and local anaesthetic, which otherwise would only act segmentally [16, 17].

Level I evidence from systematic reviews confirm that low dose ketamine when combined with morphine not only reduced pain intensity but also improved wakefulness and PONV when compared with the higher dose of morphine alone [3, 14]. This is despite a significant number of clinical trials (17 of 38, 45%) demonstrating no benefit of adding ketamine to the existing standard practice opioid analgesia. The intensity of pain, type of surgery, other co-analgesics used and the ketamine administration protocol may have influenced the results of those clinical trials. Ketamine should be considered when post-operative pain requires large doses of opioids, such as major abdominal and thoracic surgery [13].

Ketamine and Opioids

Opioid escalation in acute pain can sometimes be futile, with inadequate pain control despite very high doses. In addition, some types of pain, particularly central neuropathic and vascular ischaemic pain, can be refractory to opioid therapy. Ketamine is well described in a number of clinical trials for pain refractory to high-dose opioids. Such use is based on preclinical data demonstrating an important role for the NMDA receptor in opioid-induced hyperalgesia and in persistent pain from inflammation, nerve injury and cancer [5, 8].

Ketamine is also useful to reduce the area of punctuate mechanical hyperalgesia surrounding the surgical incision for several days after surgery. While the significance of acute hyperalgesia may be related to progression to chronic pain, the

pre-emptive administration of ketamine also consistently decreases the post-operative morphine consumption. Whether the mechanical hyperalgesia is related to the opioid administration (OIH) or occurs *de novo* remains unknown. Irrespective of the cause of this pro-nociception ketamine is probably the most potent anti-hyperalgesic available for clinical use. This has been clearly demonstrated after abdominal surgery and lasts for 48 h after ketamine anaesthesia. This anti-hyperalgesic mechanism is not fully appreciated but supports the pre-emptive and persistent analgesic effect of ketamine [16, 17].

There has been considerable interest in the combination of ketamine with the peri-operative opioids administered. Opioids are traditionally used as a part of general anaesthesia and for the treatment of acute post-operative pain. Recent research indicates that opioids produce not only analgesia, but also hyperalgesia. Consequently, peri-operative (pre, per, and post-operative) opioids may paradoxically increase post-operative pain and opioid requirements. Central sensitization includes an altered processing of innocuous, tactile impulses from myelinated afferents so that activation of these fibres produces painful sensations. The neurophysiological and biochemical mechanisms of these alterations include a decrease in inhibitory input or an increase in synaptic efficacy or membrane excitability, mediated by wind-up and neurokinin and N-methyl-D-aspartic acid receptor mechanisms (NMDA receptors) [18].

In the post-operative period, opioid containing intravenous patient-controlled analgesia (PCA) are frequently used for analgesia [19, 20]. The addition of ketamine to the morphine PCA has been described in a number of clinical trials. The concerns for the stability of these drugs have also been addressed [20]. Intravenous patient-controlled analgesia (PCA) with subanaesthetic ketamine and morphine dosaging following transthoracic lung and heart surgery has been shown to result in lower pain scores, reduced morphine consumption, shorter post-operative IV-PCA dependence, associated cardiovascular stability and better respiratory parameters. The potentiation of opioid-induced analgesia and the opioid-sparing effect of ketamine were observed in paediatric patients [21]. The parameters of the PCA settings: opioid bolus size, lockout intervals and hourly limits remain unchanged. In some situations, continuous infusion of the combination of morphine and ketamine delivered by the PCA will be better than either the opioid alone or a PCA approach alone, because of a stable NMDA receptor block [19]. We emphasize that the magnitude of the PCA bolus may need to be adapted to the individual patient, according to analgesic efficacy and side effects. The ratios described in these studies vary, but the most frequently described one is of morphine: ketamine in 1:1 ratio [19, 21]. (See further details in section Practical Application below.)

Benefits of Post-operative Ketamine

It has been a challenge to consistently demonstrate an effect of ketamine on pain scores. This again may be due to the type of surgery, ketamine dosing protocol, other multimodal analgesia drugs and/or clinical measurements. Some studies have

shown a larger improvement in dynamic pain scores, while others show both rest and dynamic pain improvements [16]. The other major benefit of ketamine observed is a reduction in opioid analgesic consumption [2, 5, 21].

This interaction of ketamine with opioids may become clinically relevant especially when pain is poorly controlled or increasing opioids are required to provide adequate analgesia.

Preclinical studies have reported that opioid mu receptor activation leads to a sustained increase in glutamate synaptic effectiveness at the level of NMDA receptors. Opioids when used alone in large doses for a prolonged period induce tolerance, which may also lead to increased post-operative pain. Ketamine, by blocking these NMDA receptors, can reduce pain, opioid requirements and prevent the development of tolerance. This has been studied extensively in animals and consistently produced positive results.

This is one of the fundamental concepts that has led to the use of ketamine as an adjuvant to opioids in multiple clinical trials and consolidated the position of ketamine in the multimodal analgesia paradigm [13]. In the study by Choe et al. administration of morphine and ketamine prior to surgery reduced the need for supplemental analgesics [9].

There are other benefits of the concomitant administration of low-dose morphine and ketamine. Studies have shown that in combination these drugs improve the adequacy of respiration measured by the oxygen saturation (SpO_2) level. This may be secondary to pain reduction thus enabling patients to breathe more deeply, cough better, and maintain adequate minute ventilation with only negligible upper-airway obstruction compared with heavily (opioid) sedated post-operative patients. In the same study, because morphine did not control pain as well as the combination of morphine and ketamine did, SpO_2 in the morphine-alone group also remained lower. In addition, ketamine characteristically increases respiratory muscle tone, which could have also contributed to airway patency and better SpO_2, even though a sub-anaesthetic dose of ketamine was applied. All the above-mentioned reasons could also have contributed to the maintenance of a normal respiratory rate and depth in the patients receiving a combination of morphine and ketamine [6].

This is an important clinical caveat—the metaphoric ‘double-edged sword’ of pain management in abdominal surgery—incisional pain prevents adequate respiration; its treatment with opioids can also lead to sedation and respiratory depression. Low dose or ultra-low dose ketamine can reduce pain without sedation or respiratory depression and should therefore be a standard part of the multimodal analgesia for abdominal surgery.

Even in patients with high risk of respiratory depression, secondary to obesity and sleep apnoea, ketamine in combination with other intravenous agents is being used to provide opioid-free anaesthesia (OFA). Another significant benefit of this OFA technique is the reduction in PONV which again indirectly implies the contribution of opioids to this gastrointestinal side-effect [22]. A trend toward less PONV is seen in patients receiving ketamine and these reductions in PONV parallel the decreased opioid consumption and improved analgesia seen with ketamine [6, 13, 14].

Hyperalgesia and Progression to Chronic Pain

The prompt and sustained abolition of pain resistance to morphine by a single bolus injection of morphine and ketamine in up to 65% of the treated patients has been well documented [6]. At the same time they observed when comparing the total dose of morphine in both groups that the effect of ketamine was greater than additive. This supports the contention of an interaction of ketamine with NMDA receptors that could have been activated by either or both of the peri-operative nociceptive inputs and by the administration of morphine.

The smallest ketamine plasma concentration to counteract hyperalgesia while producing minimal side effects was shown to be 60 μg/mL. This concentration has been achieved by giving an initial bolus dose of ketamine 0.5 mg/kg, followed by a continuous infusion of 0.12 mg/kg/h. The average ketamine consumption in many studies is significantly lower which might explain some of the negative clinical trial results in terms of pain scores and/or analgesic consumption.

When given in the sub-anaesthetic or 'low' dose, intra-operative ketamine is known to reduce mechanical hyperalgesia and improve post-operative analgesia. Even a small dose of ketamine given before skin incision decreases post-operative pain and reduces morphine consumption after open renal surgery [16]. A small intravenous dose of ketamine before the first incision followed by a 24-h infusion had a morphine-sparing effect after total hip arthroplasty and decreased post-operative chronic pain up to 6 months after surgery [21].

The effect of adding ketamine to opioids or multimodal analgesic regimens on wound hyperalgesia has been reported in clinical trials. Wound hyperalgesia was evaluated by punctuate mapping with Von Frey hair filaments and pressure pain detection thresholds. The area of hyperalgesia tested by Von Frey hair filament was significantly less in ketamine groups in a majority of trials. Though the clinical implication of hyperalgesia remains poorly understood and not well studied, it is an indicator of central sensitization. It has been hypothesized that a reduction in the area of hyperalgesia could be a measure of the prevention of central sensitization by ketamine. The reduction in the area of hyperalgesia may not be associated with improvement in acute post-operative pain outcome measures, but may decrease the persistence of wind-up pain at 7 days [23]. When followed up at 2 weeks, 1 and 6 months and 1 year after surgery, patients who received IV ketamine had significantly reduced long-term pain [24]. It may also be worthwhile to note that all patients studied by these investigators had undergone surgery for rectal adenocarcinoma, a typically difficult pain model to treat. Thus, even without any effect on acute nociceptive pain, low-dose ketamine may have a role in reducing pathological pain, which in these patients was chronic, neuropathic and malignancy related.

Apart from patients with malignancy related surgery, patients undergoing surgical procedures which are associated with the risk of development of chronic post-operative neuropathic pain such as thoracotomy and amputation, will benefit from peri-operative ketamine [13].

Another group of patients who may benefit from peri-operative ketamine are those who have already developed chronic pain and/or those who are opioid tolerant. Loftus et al. demonstrated that intra-operative preventative ketamine reduces opiate consumption in the acute post-operative period by 37% in opiate-dependent patients with chronic pain who are undergoing painful back surgery. In addition, it seems to reduce pain intensity post-operatively in the PACU and at 6 weeks as well as reduced morphine consumption at the first post-operative visit. The results of these trials have shown that intermediate and long-term outcomes produced by the addition of ketamine was far superior to that produced by opioid analgesics [12]. Other than the reduction in pain intensity at 6 weeks, research has also found significantly less antidepressant use at the first post-operative visit compared with placebo, despite no significant difference between groups pre-operatively [12].

Understanding the utility of preventative NMDA receptor antagonism in patients with a history of chronic pain has also led to its use in patients on chronic opiate medication. This has been suggested as a primary target for future research. It is well known that patients with chronic pain and chronic opioid use are at increased risk of suboptimal post-operative pain management and consequently at increased risk of cardiopulmonary complications and further exacerbation of existing chronic postsurgical pain [12].

Influence on Carcinogenesis

In addition to their analgesic effects, opioids have well established immune-modulatory effects. Despite experimental and animal studies implicating peri-operative opioids in cancer metastasis and recurrence the evidence from clinical trials are conflicting. It is theorized that various agents (anaesthetics, analgesics, blood transfusions etc.) activate specific genes during the peri-operative period, which may contribute to cancer recurrence and metastasis [25].

Ketamine is known to exhibit immuno-modulatory effects on macrophages, lymphocytes, and mast cells in experimental studies. Despite its inhibition of the dendritic cell-mediated maturation of T cells in a mouse model, it must be noted that the ketamine concentration used was two to three times higher than that used in human clinical setting. One study reports the effect of low-dose ketamine (0.15 mg/kg) on immune function in patients undergoing elective abdominal surgery [26]. It indicated that ketamine attenuated production of the proinflammatory cytokines, IL-6 and TNFα, and suppressed NK cell cytotoxicity after operation. The clinical relevance of these findings is not fully understood [25, 26].

The contribution of other factors (especially opioids) on immune-modulation, neuro-endocrine and inflammatory response influencing tumor metastasis and/or recurrence cannot be ruled out. Nevertheless, ketamine offers a promising non-opioid option in abdominal surgery and until further evidence in this area becomes available, is probably safe (and safer than opioids alone) to administer to patients with abdominal surgery, especially those with malignancies [25].

Other Benefits of Ketamine

Another reported benefit of ketamine is in the treatment of post-operative shivering with a faster onset than meperidine at ultra-low dose (<0.1 mg/kg) [27]. Low-dose ketamine is commonly used to treat distressing states such as anxiety and depression [28]. It is unclear whether changes in stress hormone concentrations are beneficial or harmful in pain and depression. This study found that even at low doses, ketamine doubles cortisol production [29].

Side Effects

Widespread use of ketamine has been limited by clinicians' concerns about adverse effects such as dysphoria, hallucinations, and dissociative symptoms. Furthermore, the dosing of ketamine is inconvenient in chronic pain patients as it is relatively short acting and is unavailable in an oral formulation [5].

The side effects of ketamine have been described in the preceding sections. Whilst these are dose dependant, some patients demonstrate intolerance to the central nervous system side effects i.e. sedation, nausea and vomiting, catalepsy and locomotor depression, dependence and tolerance [8]. Side effects from ketamine were more commonly observed at higher doses and sedation is commonly described at these doses [30].

It has been observed in healthy human volunteers that high dose ketamine can significantly alter mood states and produce dose-related impairment of sensory perception or even impact the process of sensory integration [6]. It has been reported that more than one third of the patients may experience unpleasant dreams or acute psychosis-like symptoms that may or may not be associated with hallucinations on emergence when anaesthetic doses (1–3 mg/kg) of ketamine are administered. Sub-anaesthetic doses (0.1–1 mg/kg) of ketamine in healthy human volunteers can produce subtle cognitive dysfunction, e.g., attention-free recall and recognition memory. Clinical studies in patients with acute pain receiving such sub-anaesthetic doses showed no changes in cognition, perception, or mood swings in any patients even 24 h after ketamine administration [6]. This difference can be explained by the fact that the healthy volunteers are different from the patients experiencing acute pain. Consequently, patients who do not have poorly controlled pain or acute hyperalgesia should not be prescribed ketamine—they may experience adverse side-effects without any clinical benefit.

It is probably important to note that many of the central nervous system side effects (dizziness, diplopia, dysphoria, dreams, hallucinations disorientation, strange sensations, light headedness, sleep difficulties, and confusion) described in ketamine-treated patients is also seen with opioids.

Making a clear distinction between the etiologies of these presentations, especially in patients receiving both opioids and ketamine, may be clinically challenging, if not impossible.

Practical Considerations

Intra-operative Ketamine

A novel method of ketamine administration during surgery was developed at our center. We combine ketamine with fentanyl and lidocaine and infuse this 'cocktail' (called fentaketacaine or FLK) during surgery under general anaesthesia.

At or after induction, patients identified as appropriate for ketamine (and lidocaine) receive 0.2–0.5 mg/kg (max 20 mg IV) followed by lidocaine (1–2 mg/kg, max 100 mg IV). We then initiate an infusion of FLK (syringe containing Fentanyl 10 μg/mL + Lidocaine 10 mg/mL + Ketamine 1 mg/mL). This is prepared by taking a 20 mL syringe and adding 200 μg Fentanyl (4 mL of 50 μg/mL), 200 mg Lidocaine (10 mL of 2%), 20 mg ketamine (2 mL of 10 mg/mL) and saline (4 mL) to make it a total of 20 mL. We program the pump as though there is only lidocaine 10 mg/mL in the syringe at 1–2 mg/kg/h. Because of the ratios in the mixture, the pump will also deliver Fentanyl 1–2 μg/kg/h. and Ketamine 0.1–0.2 mg/kg/h. The infusion rate can be reduced or increased depending on the haemodynamics. For obese and morbidly obese patients, it is important to use their ideal body weight (IBW). Additional boluses of ketamine, lidocaine or longer acting opioids are rarely required, unless the patient is opioid tolerant or is demonstrating other signs of inadequate analgesia. There may be an anaesthetic (MAC) sparing effect and it may be advisable to monitor the depth of anaesthesia, especially in long procedures and/or vulnerable patients (younger, older, past history etc.).

This infusion of FLK can be continued for 4–6 h without accumulation and usually stopped at or before wound closure. Patients usually wake up comfortably, especially after laparoscopic procedures and some will require early post-operative resumption of their multimodal analgesia, including titration of longer acting opioids. The two main indications for the use of FLK are (1) alternative to epidurals and (2) difficult-to-treat pain patients. These indications have been elaborated in Table 5.1.

Post-operative Ketamine

It is often challenging to achieve good quality analgesia following abdominal surgery. While epidural analgesia and other regional anaesthesia techniques described

Table 5.1 Indications for intra-operative ketamine as fentaketacaine (FLK) infusion

1. Alternatives to epidurals
• Epidural contraindicated, refused or failed
• Epidural attempted, inadequate or not tolerated
• Epidural not done—minimally invasive (laparoscopic) surgery
2. Difficult-to-treat pain
• Surgery at a site of chronic pain
• Chronic pain elsewhere, e.g., fibromyalgia
• Opioid-use, abuse, dependence or tolerance
• Poorly controlled pain: acute hyperalgesia
• Experience in past of poorly controlled pain

elsewhere in this book are very useful, they are not always possible, may fail or become inadequate. Two of the frequently encountered side effects with opioid based analgesia are respiratory depression and post-operative nausea and vomiting (PONV). These may have a significant impact on the recovery of patients after abdominal surgery. After any surgery, especially abdominal surgery, the patient may remain in a fasting state (NPO) and have enteral drainage or feeding tubes that would preclude the use of the gut for oral/enteral multimodal analgesia. As described in the chapter on lidocaine, parenteral multimodal analgesia based on the WHO step ladder (step-wise, severity-based and opioid-sparing) with adequate anti-pronociception is vital to ensure high quality analgesia with low side effects.

It is in this context that ketamine (and lidocaine) are essential parts of the acute pain management armamentarium for abdominal surgery. While the use of lidocaine is described in detail elsewhere, the use of the DN4 questionnaire will be useful to determine the need to add ketamine to the post-operative plan. As discussed previously, ketamine is a very potent anti-hyperalgesic and is clearly indicated to treat both mechanical and opioid-induced hyperalgesia. The other patients who would benefit from post-operative ketamine include those with poorly controlled pain, failed or inadequate epidural or other regional anesthesia techniques, opioid escalation or side-effects especially ileus, nausea/vomiting, sedation and respiratory depression, opioid tolerant or dependant, chronic neuropathic/non-cancer pain or malignancy related pain.

One of the most effective and safe ways of administering ketamine in the post-operative period is via a PCA system. With ketamine delivered in a fixed ratio with the parenteral opioid. Ketamine administered via the PCA allows the patient to self-titrate their requirements within a safe hourly limit. This in turn decreases opioid use and associated side-effects, decreases the need for health care provider intervention and empowers the patient with a sense of autonomy. Moreover, as discussed above, the indications for ketamine in the post-operative period includes patient and procedural indications that are otherwise poorly controlled with opioids alone (Table 5.2). Adding ketamine to the opioid PCA therefore provides excellent analgesia with improved patient safety and satisfaction.

At our center, two morphine-ketamine ratio choices were made available as a premixed solution for use in the PCA. These ratios served to accommodate a wide range of opioid requirements, without exceeding a fixed amount of ketamine

Table 5.2 The Ottawa Hospital (TOH) Acute Pain Service (APS) indications for adding ketamine to IV PCA

1. **T**rauma: multiple and/or major injuries; burns, degloving and crush injuries, rib fractures
2. **A**cute Pain: poorly controlled, acute on chronic pain, prevention of Chronic Post-Surgical Pain (CPSP), opioid tolerance and/or dependence, substance abuse
3. **N**europathic pain: acute hyperalgesia opioid induced or opioid resistant, malignancy related, vascular insufficiency and ischemia, sickle cell crises etc.
4. **G**astro-Intestinal Surgery: with or without epidural analgesia, laparoscopic procedures and laparoscopic converted to open, ERAS
5. **O**bese, OSA and elderly: sensitive to opioids or having opioid side effects

available for use on demand. The general principle is to keep the hourly dose of intravenous ketamine to less than 10 mg/h. At this ultra-low dose the patient would benefit from the NMDA antagonist anti-hyperalgesic effects while avoiding the psychomimetic side-effects. In our extensive experience of over 15 years, the patients whose PCA contains the morphine and ketamine combination continue to be monitored as per the opioid PCA modality and do not require any extra or special monitoring *per se*.

Morphine, 1 mg/mL, with Ketamine, 1 mg/mL, is prescribed for patients expected to use less than 10 mg/h of morphine. These would include almost all abdominal surgery in most of the opioid naïve patients. Morphine, 5 mg/mL, with ketamine, 1 mg/mL, is suggested for patients expected to require between 25 and 50 mg/h of morphine on an ongoing basis (i.e., >12 h). This would be used in opioid-tolerant patients, polytrauma patients, those with vascular ischemia and those with malignancy related pain. Even when using the ketamine PCA mixtures, the orders and the pump program remains unchanged with *bolus*, *lockout*, *basal* and *hourly limit* set according to the morphine requirement.

For opioid-tolerant patients or others with poorly controlled pain, it is preferable to increase the bolus size and hourly limit, rather than change the lockout or add a basal infusion [20]. The variable magnitude of the bolus dose was probably the result of the well-known interindividual variability in drug requirement to achieve satisfactory analgesia.

The use of ketamine requires careful consideration in patients at particular risk for respiratory depression from conventional opioid-only, e.g., morbidly obese patients, those with suspected OSA and or untreated OSA, elderly and renal insufficiency. Extended or increased cardiorespiratory monitoring may be required for these patients, especially until their pain is well controlled.

Also of importance to note is that when ketamine is added to the post-operative pain management, pain scores and consequently opioid requirements can fall dramatically. It is therefore pertinent to monitor these patients and reduce any fixed dose or long-acting opioids that they may be receiving. If sedation, respiratory depression or any other signs or symptoms of opioid overdose occur after the ketamine is started, they should be treated as per standard opioid overdose guidelines.

In some situations, especially in intensive care and other monitored areas, ketamine can also be administered as a continuous intravenous infusion. This is most likely to provide stable antihyperalgesia, but less likely to provide situational analgesia as required by the patient. In our experience this has been useful in sedated, intubated and ventilated patients in the critical care areas. Again, the aim would be to keep the hourly limit of ketamine to less than 10 mg/h.

Conclusions

The combination of our understanding of the pharmacology, vast clinical experience and the available evidence support a wide role for the use of ketamine in the peri-operative period. Ketamine is useful as a co-analgesic and anti-hyperalgesic thereby decreasing post-operative pain, opioid analgesic requirements and opioid related side-effects following major abdominal surgery. Low and ultra-low

dose ketamine can be used as an infusion during surgery. Post-operatively it may be added to an opioid for PCA use. This will assist the patient in achieving their ERAS goals, i.e., early mobilization, early nutrition and discharge with improved satisfaction.

References

1. Tawfic QA. A review of the use of ketamine in pain management. J Opioid Manag. 2013;9:379–88.
2. Himmelseher S, Durieux ME. Ketamine for perioperative pain management. Anesthesiology. 2005;102:211–20.
3. Ding X, Jin S, Niu X, Wang T, Zhao X, Ren H, Tong Y, Li Q. Morphine with adjuvant ketamine versus higher dose of morphine alone for acute pain: a meta-analysis. Int J Clin Exp Med. 2014;7:2504–10.
4. Blanke ML, Vandongen AMJ. Activation mechanisms of the NMDA receptor. In: Van Dongen AM, editor. Biology of the NMDA receptor. Boca Raton, FL: CRC Press; 2009. Chapter 13.
5. Grande LA, O'Donnell BR, Fitzgibbon DR, Terman GW. Ultra-low dose ketamine and memantine treatment for pain in an opioid-tolerant oncology patient. Anesth Analg. 2008;107: 1380–3.
6. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesth Analg. 2003;96:789–95.
7. Tawfic QA, Eipe N, Penning J. Ultra-low-dose ketamine infusion for ischemic limb pain. Can J Anaesth. 2014;61:86–7.
8. Romero TR, Galdino GS, Silva GC, Resende LC, Perez AC, Côrtes SF, Duarte ID. Ketamine activates the L-arginine/nitric oxide/cyclic guanosine monophosphate pathway to induce peripheral antinociception in rats. Anesth Analg. 2011;113:1254–9.
9. Choe H, Choi YS, Kim YH, Ko SH, Choi HG, Han YJ, Song HS. Epidural morphine plus ketamine for upper abdominal surgery: improved analgesia from preincisional versus postincisional administration. Anesth Analg. 1997;84:560–3.
10. Slogoff S, Allen GW, Wessels JV, Cheney DH. Clinical experience with subanesthetic ketamine. Anesth Analg. 1974;53:354–8.
11. Waxman K, Shoemaker WC, Lippmann M. Cardiovascular effects of anesthetic induction with ketamine. Anesth Analg. 1980;59:355–8.
12. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, Beach ML. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010;113:639–46.
13. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg. 2004;99:482–95.
14. Laskowski K, Stirling A, Mckay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth. 2011;58:911–23.
15. Zakine J, Samarcq D, Lorne E, Moubarak M, Montravers P, Beloucif S, Dupont H. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesth Analg. 2008;106: 1856–61.
16. Kararmaz A, Kaya S, Karaman H, Turhanoglu S, Ozyilmaz MA. Intraoperative intravenous ketamine in combination with epidural analgesia: postoperative analgesia after renal surgery. Anesth Analg. 2003;97:1092–6.
17. Aida S, Yamakura T, Baba H, Taga K, Fukuda S, Shimoji K. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: a randomized double-blind study. Anesthesiology. 2000;92:1624–30.

18. Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). Acta Anaesthesiol Scand. 2005;49:1405–28.
19. Sveticic G, Farzanegan F, Zmoos P, Zmoos S, Eichenberger U, Curatolo M. Is the combination of morphine with ketamine better than morphine alone for postoperative intravenous patient-controlled analgesia? Anesth Analg. 2008;106:287–93.
20. Schmid R, Koren G, Klein J, Katz J. The stability of a ketamine-morphine solution. Anesth Analg. 2002;94:898–900.
21. Lee SK. The use of ketamine for perioperative pain management. Korean J Anesthesiol. 2012;63:1–2.
22. Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. Br J Anaesth. 2014;112:906–11.
23. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand. 1997;41:1124–32.
24. De Kock M, Lavand'Homme P, Waterloos H. 'Balanced analgesia' in the perioperative period: is there a place for ketamine? Pain. 2001;92:373–80.
25. Lee BM, Cata JP. Impact of anesthesia on cancer recurrence. Rev Esp Anestesiol Reanim. 2015;62:570–5.
26. Heaney A, Buggy DJ. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis? Br J Anaesth. 2012;109(Suppl. 1):i17–28.
27. Dal D, Kose A, Honca M, Akinci SB, Basgul E, Aypar U. Efficacy of prophylactic ketamine in preventing postoperative shivering. Br J Anaesth. 2005;95:189–92.
28. Parsaik AK, Singh B, Khosh-Chashm D, Mascarenhas SS. Efficacy of ketamine in bipolar depression: systematic review and meta-analysis. J Psychiatr Pract. 2015;21:427–35.
29. Khalili-Mahani N, Martini CH, Olofsen E, Dahan A, Niesters M. Effect of subanaesthetic ketamine on plasma and saliva cortisol secretion. Br J Anaesth. 2015;115:68–75.
30. Kose EA, Dal D, Akinci SB, Saricaoglu F, Aypar U. The efficacy of ketamine for the treatment of postoperative shivering. Anesth Analg. 2008;106:120–2.
31. Brookoff D. Chronic pain: a new disease? Hosp Pract (Off Ed). 2000;35:45–52. 59