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Proposal for practice guideline
Low dose ketamine infusion in the management of chronic non-cancer pain

Contents

Faculty of Pain Medicine
Australian and New Zealand
College of Anaesthetists

Executive Summary

1. There is substantial clinical variation in the use of ketamine infusions for chronic non-cancer pain.

2. There is a paucity of quality evidence concerning the use of ketamine infusions in patients with chronic non-cancer pain.

3. The rationale for such practice is elusive, the possibilities including:
   - harnessing an intrinsic analgesic effect from ketamine
   - inducing reversal of inferred central sensitisation of nociception
   - facilitating reduction in opioid usage

4. It is difficult to distinguish in the literature the relative priorities of reduction in pain and reduction in opioid dosage achieved by ketamine infusion.

5. Questions remain to be addressed, concerning the rationale of this procedure, including but not limited to:
   - Does ketamine infusion facilitate improvement in function?
   - Can ketamine infusion reverse established central sensitisation of nociception?
   - Does ketamine infusion prevent relapse of opioid misuse?
   - Is there an advantage of ketamine infusion over controlled reduction in oral or transdermal opioid?

6. Principles to guide the administration of ketamine infusions include:
   a. Clear articulation of the purpose(s) of ketamine infusion
   b. Strict eligibility criteria for patient selection
   c. Comprehensive sociopsychobiomedical assessment of patients before and after infusion
   d. Adherence to agreed protocol of delivery of infusion
   e. Plan for reduction regimen of existing opioid analgesic medications
   f. Clear pathway for follow-up
   g. Clear line(s) of communication with patients' primary health practitioner(s)

Literature review

A. Ketamine in "chronic pain"

1. Hocking G, Cousins MJ. Ketamine in Chronic Pain Management: An Evidence Based Review. *Anesthesia and Analgesia* 2003; 97: 1730.

Search: 1996-August 2002
Studies found: 11 controlled; many uncontrolled
Syndromes treated: central pain, complex regional pain syndrome, fibromyalgia, ischaemic pain, nonspecific pain of neuropathic[1] origin, acute-on-chronic neuropathic pain, orofacial pain, phantom/stump pain, post-herpetic neuralgia
Mode: Parenteral administration, i.v. or s.c. 0.125-0.3mg/kg/hr ("optimal")

- Comment: "The magnitude of reported benefit from ketamine in chronic pain is often little

[1] Note that the definition of neuropathic pain was changed in 2011. It is very likely that many of the "neuropathic syndromes" studied in articles published before 2011 (if not also later) would not satisfy the current definition.

more than what could be expected by a placebo effect. It is therefore unlikely that ketamine will become a regular treatment option for patients with chronic pain, unless there is greater interest in performing good quality studies in this area to further delineate the target population and dose response for specific diagnoses. Until this takes place, ketamine will remain a third line drug that is administered on the basis of weak evidence in patients who have failed to respond to routine pharmacotherapy."

2. Visser E, Schug SA.The role of ketamine in pain management. *Biomed Pharmacother* 2006; 60:341-8.

- Comment: "The place of ketamine in the treatment of chronic pain and the effects of long-term medicinal use remain unclear."

3. Bell RF. Ketamine for chronic non-cancer pain (Topical review). *Pain* 2009; 141:210-214

Search: up to 2008
Studies found: 29 controlled trials with 579 patients; 18 intravenous; duration in 21 trials <4h
Syndromes treated: chronic neuropathic pain (incl phantom limb) pain, whiplash-asssociated pain, TMJ arthralgia, atypical odontalgia, breakthrough pain, migraine prophylaxis

- Comment: "In summary, while the current literature provides evidence for acute relief of chronic non-cancer pain, information supporting the efficacy and tolerability of ketamine in the long-term treatment of chronic pain is extremely limited."

4. a) Noppers I, Niesters M, Aarts L, Smith T, Sarton E, Dahan Ketamine for the treatment of chronic non-cancer pain. (Review) *Expert Opin Pharmacother* 2010; 11:2417-2429

   b) Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits (Review) *Br J Clin Pharmacol* 2013; 77:357–367

   c)Sigtermans MJ, Van Hilten JJ, Bauer MCR, Arbous MS, Marinus J, Sarton EY, Dahan A. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. (RCT) *Pain* 2009; 145:304-311.

4. (a,b)

Search: 1992-2010
Studies found: 36 RCTs, 6 since 2008; 21 intravenous; > 0.15 mg/kg ketamine
Syndromes treated (text refers to them as "neuropathic"): acute and chronic migraine (2), breakthrough non-cancer pain (1), central neuropathic pain (2), chemotherapy- induced neuropathy (1), chronic neuropathic pain (various causes) (9), complex regional pain syndrome (3), fibromyalgia (3), painful limb ischaemia (3), peripheral nerve injury (traumatic) (4), phantom limb pain (1), post-herpetic neuralgia (1), spinal cord injury (2), temporomandibular pain (2), trigeminal neuropathic pain (1), whiplash (3)

- Comment: Majority of studies demonstrated > 50% reduction of pain intensity; effect did not persist beyond 48 h following infusion. Infusion duration ranged from 30 min to 2 h; no consensus on administration protocol.
- Speculation [in 2(c)]: "Our analysis indicates that at an infusion duration > 10 h the probability of an effect lasting > 48 h approaches 95%, while at durations > 30 h the probability approaches 99%. Note, however, that following infusion analgesia slowly dissipates over time. This indicates that these infusion paradigms were insufficient to cause a permanent reduction of pain. Possibly other infusion regimens (e.g., regular 10-h infusions, daily 1- to 2-h infusions) may have a more permanent effect. None of the published RCTs addressed this issue."

5. Randomised controlled trials

Three RCTs on long-term intravenous infusion published after 2008 (see Sigtermans et al, 2009; Schwartzmann et al, 2009; Amr, 2010) all used a multiple day infusion scheme.

(a) Sigtermans et al, 2009:

- 30 patients (disease duration: mean 7.4 years, range 0.1 - 32 years; mean baseline pain score 7.2 on a scale of 0 - 10)
- 4.2-day continuous infusion of ketamine; mean dose of 22±2 mg/h/70kg.
- Significant analgesic effects observed during 4.2-day treatment phase (pain score 2.7 vs 5.5).
- Over the 12-week duration of the study, "ketamine modulated the course of chronic pain more favorably than placebo".
- No improvement in function
- Cost of the intensive and long-term in-house treatment
- Ketamine-related side effects included nausea/vomiting and psychotropic effects.
- "Twenty patients who initially received placebo were allowed to receive the identical ketamine treatment, but now in an open-label fashion. As expected, their analgesic responses were larger by 1 NRS point at 2 weeks and pain relief > 50% lasted for > 3 weeks (Figure 3). This suggests that a large proportion of the response seen in this patient group is expectancy-related."

b) Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain* 2009; 147: 107–15. [See also Commentary in *Pain* 2010; 150:10-11]

- Daily 4-h IV ketamine infusions (max. dose 0.35 mg/kg/h) for 10 days
- Subjects in both arms of the study received clonidine and midazolam.
- Subjects receiving ketamine had consistent decreases for all pain-related parameters that lasted for the 12-week post-treatment evaluation period (total McGill pain score pretreatment = 23.1, post treatment weeks 1-2=16.2, post weeks3-4=13.4 and post weeks 9-12= 15.4
- Study stopped after 19 patients (9 in the ketamine arm and 10 in placebo arm) as authors had observed greater pain relief with a higher dose of ketamine than allowed in the protocol (max. dose 25 mg/h) in an open-label study.

c) Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial.
Pain Physician 2010;13:245-9

- Group 1 (n = 20): 80 mg intravenous ketamine (? dose) over 5 h daily for 7 days plus 300 mg gabapentin three times daily;
- Group 2 (n = 20): 5-h placebo infusion once daily plus 300 mg gabapentin three times daily.
- Pain relief was significantly greater in Group 1 relative to Group 2 during infusion and during the first 2 weeks following infusion.
- Thereafter no more differences between treatment groups in pain scores
- Pain scores remained decreased versus baseline for 4 weeks following the end of treatment in both groups.

6. Systematic review and meta-analysis

Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice ASC, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *The Lancet Neurology* 2015; 14:162-173.

- Ketamine and other NMDA-antagonists: inconclusive recommendations for use or recommendations against use based on the GRADE classification

7. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J (eds). *Acute Pain Management: Scientific Evidence,* 4E. Melbourne: Faculty of Pain Medicine and Australian and New Zealand College of Anaesthetists, 2015.

- "In view of the risks…current use of ketamine to treat chronic pain should be restricted to therapy-resistant severe neuropathic pain" (p. 118).

B. Ketamine as "opioid-sparing"

8. Pain of acute nociception

Ketamine has an established place in the perioperative management of acute pain (at subanaesthetic doses <0.5 mg/kg), where it has consistently been shown to be opioid sparing and to decrease nausea and vomiting while adding only a mild side-effect profile of its own. The optimal dose is unresolved.

9. Pre-emptive analgesia in acute nociception

A significant body of evidence has tested the hypothesis that pre-emptive administration of ketamine might prevent the development of pain (both acute and chronic) by preventing the sensitisation of neuronal circuits. Although positive findings were reported from animal studies, data from human trials have not shown a clear pre-emptive benefit. However, the acute analgesic effects of ketamine can outlast the expected duration of the effect of the drug (>5.5 half-lives), suggesting that ketamine has a preventive effect. This is also confirmed by data that show perioperative ketamine reduces the incidence of chronic postsurgical pain..

10. Ketamine as an agent to reduce opioid requirement in chronic pain: "improvement of opioid efficacy"

a) Kapural L, Kapural M, Bensitel T, Sesslet DI. Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements. *Pain Physician* 2010; 13: 389-394

- retrospective chart review, n=18, with controls
- 10-100 mg/hr, 3+ hrs, 3-6 weeks; co-administered with midazolam
- 11 patients completed 3-6 weekly ketamine infusions 5 of 11 maintained <50% baseline opioid use at 6/12
- no differences in pain scores between ketamine and control groups

b) Quinlan J. The use of a subanesthetic infusion of intravenous ketamine to allow withdrawal of medically prescribed opioids in people with chronic pain, opioid tolerance and hyperalgesia: Outcome at 6 months. *Pain Med* 2012; 13: 1524 [Letter]

- retrospective, >6/12 post infusion, 11 responses of 15
- 2.5-40 mg/hr SC; 5 days
- 8/11 "better" at 2/12; 3/11 "well" and off opioids at 6/12

c) Jovaiša T, Laurinenas G, Vosylius S, Šipylaite J, Badaras R, Ivaškevicius J Effects of ketamine on precipitated opiate withdrawal. *Medicina* (Kaunas) 2006; 42: 625-634

- Ketamine used to influence naloxone-induced withdrawal under general anaesthesia
- Clonidine, carbamazepine, clonazepam post op

- n=50; OME ~60mg/day
- ketamine associated with better control of withdrawal; no differences at 4/12
- no mention of pain.

Literature summary: state of the science; state of the art

Despite a paucity of quality evidence, the use of ketamine in chronic non-cancer pain is apparently widespread, on a quite empirical basis.

The rationale is elusive, the possibilities including:

- intrinsic analgesic effect, which is unlikely at the doses used
- reversal, even temporary, of inferred central sensitisation of nociception
- facilitation of reduction in opioid usage, itself context-dependent, and so unlikely to persist meaningfully beyond duration of infusion

It is difficult to distinguish in the literature between the desired outcomes of reduction in pain and reduction in opioid dosage; the emphasis appears to be the latter.

A number of questions arise:

- Does ketamine facilitate improvement in function?
- Can ketamine be “antihyperalgesic” in established central sensitisation states?
- How does temporary reduction in opioid usage (which is not the same as “enhancement of analgesia”) affect the underlying drivers of the experience of pain?
- Does ketamine prevent relapse of opioid misuse?
- As it does not address the context of opioid misuse, why is ketamine preferred to controlled opioid reduction?

Proposal for best practice in low-dose ketamine infusion in the management of patients with chronic non-cancer pain

1. Purpose

In patients experiencing chronic non-cancer pain who are poorly responsive to opioid analgesics and/or are experiencing clinically significant opioid side-effects:

- to facilitate reduction (if not withdrawal) in opioid dose per se
- to facilitate a multidisciplinary approach to ongoing management
- to facilitate improved quality-of-life

2. Patient selection

Ketamine infusion may be considered in patients:

- with clear clinical evidence of central sensitisation and
- who are taking doses of opioid(s)
    - that are considered to reflect poor opioid-responsiveness; and/or
    - that are associated with clinically significant side-effects; and/or
    - that are associated with drug-seeking behaviour to the detriment of themselves and/or others

3. Comprehensive assessment in sociopsychobiomedical framework Specifically to identify and document:

- effectiveness of multidisciplinary approaches to date
- expectancy of infusion (patient’s perspective)
- goals of infusion (clinician’s perspective)

- factors that might predispose to potential harm from ketamine infusion
- indicators of success (or otherwise).

4. Context

- Multidisciplinary assessment prior to decision regarding infusion
    - assessment can be facilitated by the use of instruments such as BPI, PSEQ.
- Multidisciplinary review following infusion is recommended
    - use of the electronic Persistent Pain Outcomes Collaboration (ePPOC) dataset, or equivalent, is recommended to monitor progress
- Delivered in experienced[2] in-patient setting over 2-5 days; single room occupancy preferred
- Daily review by attending specialist pain medicine physician
- Emergency after-discharge plan, especially for recrudescence of "pain"
- Primary practitioner communication and follow-up

5. Infusion protocol

- Subcutaneous delivery via a dedicated line has lower risk of accidental bolus dosing compared with intravenous delivery with a potentially shared line
- An infusion pump, with a lockable, secure outer case is preferred
- Patients not allowed off the ward with the pump attached
- Dose
    - induction: 0.05-0.1mg/kg/hr
    - maximum: 0.5 mg/kg/hr
    - cessation: a period of weaning (12-24 hours) can be considered ahead of cessation of the infusion. After cessation the patient should be observed in hospital for a period of 4 hours prior to discharge.
- If patients report troublesome side effects, the infusion is paused for one hour then recommenced. If further side effects occur, the responsible physician is contacted for direction.
- Development of dissociative or amnestic effects results in termination of infusion

6. Concomitant management of existing opioids

- An opioid treatment plan should be negotiated with the patient prior to the admission for ketamine infusion. Depending on the context this might involve opioid reduction, cessation or switching.
- It is recommended that conversion of current opioids (oral, transdermal) to one opioid species be made prior to admission.
- Any change in opioid regimen occurring during the admission should be clearly communicated with the patient's general practitioner at discharge.
- Support to patient and general practitioner should be offered post discharge along with a plan for management of "relapse".

[2] Staffed by experienced nurses who understand the pharmacology of the drugs, infusion equipment and monitoring

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Appendix 1
Proposed mechanisms for the analgesic effect of ketamine

1. Inhibition of the N-methyl-D-aspartate (NMDA) -receptor
Ketamine is a non-competitive antagonism of the NMDA-receptor at subanaesthetic concentrations.

A central issue is whether all the clinically relevant analgesic effects of ketamine are related to NMDA-receptor antagonism.

- If so, pain relief would only be expected in situations where there is sensitization of the central nervous system.
- main role of ketamine at lower concentrations is as an antihyperalgesic/ antiallodynic or tolerance-protective drug [Visser & Schug, 2006]

2. Intrinsic analgesic effect
At higher (anaesthetic) concentrations ketamine has been reported to interact with

- opioid receptors (central and spinal)
- monoamine systems: agonistic effect on α- and β-adrenergic receptors; enhancement of dopamine activity (possibly relevant to euphorigenic, addictive and psychotomimetic properties)
- cholinergic: antagonistic at CNS muscarinic receptors

Possible other actions:

- effect on purinergic and adenosine receptor systems
- local anaesthetic effects

3. Central antinociceptive effects
Enhancement of descending inhibition (enhanced or re-activated experimental expression of descending inhibition, conditioned pain modulation), anti-inflammatory effects [Niesters, 2013]

Reduction of temporal summation in the nociception reflex model.

4 (a) Attentuation of acute opioid tolerance
“Opioid sparing” due to “attenuation of acute opioid tolerance” [Kissin et al. 2000] (Problems of definition)

4 (b) Prevention of opioid-induced hyperalgesia
Animal data indicate that NMDA receptor antagonists prevent development of opioid-induced hyperalgesia although the significance of that role is debated.

5. Cytokine effects
Inhibition of tumor necrosis factor-alpha (TNF-alpha) and interleukin 6 (IL-6) gene expressions in lipopolysaccharide (LPS)-activated macrophages has been reported.

6. Effect on depression (via BDNF)
Recent evidence suggests that ketamine has potent anti-depressant qualities; however no evidence was found for an improvement of depressive symptoms following long term ketamine treatment in CRPS patients.

Appendix 2
Clinical pharmacology of ketamine

Phenylpiperidine derivative structurally related to phencyclidine (PCP, 'angel dust') - 2(2-chlorophenyl)-2-(methylamino)-cyclohexanone
Two stereoisomers, S(+)- and R(-)-ketamine
Commercially: racemic mixture [Ketalar®, Pfizer Inc]; S(+) enantiomer [S-ketamine or Ketanest-S®, Pfizer Inc]

Pharmacokinetics

Absorption

After intramuscular administration

- Tmax 5-15 min

After oral administration

- Tmax 30 min
- bioavailability 17%; rectal bioavailability 25%;

After nasal administration

- bioavailability 50% (? due to significant swallowing)

Distribution

- high lipid solubility and low plasma protein binding (12%)
- rapid transfer across the blood-brain barrier (blood–effect site equilibration half- life, t1/2ke0, 1–10 min)

After intravenous administration

- volume of distribution 1.5 to 3.2 l/kg
- clearance 12-28 ml/(kg.min)
- distribution half-life 24s (?)
- redistribution half-life 7–15 min
- elimination half-life 2–3 h

Volume of distribution and clearance for S-ketamine are 9 and 14% greater than those for R-ketamine, respectively

Biotransformation

Biotransformation primarily takes place in the liver.

- N-demethylation to norketamine via CYP3A4, CYP2B6 and CYP2C9
- [norketamine to 4-, 5- and 6-hydroxynorketamine via CYP2A6 and CYP2B6]

When administered orally or rectally, initial plasma norketamine concentrations are higher than those of ketamine but the plasma AUC for norketamine is similar for all routes of administration. Norketamine has one-third the anaesthetic potency of ketamine and has analgesic properties. In humans, the analgesic properties of norketamine have not been studied directly.

After intravenous administration of ketamine, norketamine is produced within minutes and may exceed the ketamine concentration particularly after long term infusion. After termination of intravenous ketamine administration, ketamine concentrations drop rapidly and norketamine concentrations exceed the ketamine concentration.

Elimination

The predominant route of elimination is by liver metabolism. Elimination of norketamine and the hydroxynorketamines follows glucuronidation in the liver; conjugated hydroxy metabolites are mainly excreted renally. Terminal elimination half-life ranges from 100 to 200 minutes.

Dosages [Ref: WHO, 2006]
For anaesthesia:

- intravenous 2 mg/kg over 60 seconds usually produces surgical anaesthesia within 30 seconds lasting for 5-10 minutes (dose may range from 1 to 4.5 mg/kg); an
- intramuscular dose equivalent to 10 mg/kg (range 6.5-13 mg/kg) usually produces surgical anaesthesia within 3 to 4 minutes lasting for 12 to 25 minutes

For analgesia:

- intravenous 0.2-0.75 mg/kg

For psychotropic effects:

- intravenous 0.1-1.0 mg/kg (bolus of 0.1-0.2 mg/kg and maintenance infusion of 0.0025-0.02 mg/kg/min)
- intramuscular 25-200 mg

Dose dependent clinical outcomes:

- Anti-hyperalgesic 0.05-0.3 mg/kg/hr [origin uncertain]
- Psychomimetic effects 0.2-0.6 mg/kg/hr
- Analgesia 0.25-0.75 mg/kg
- Bronchodilation 0.5-1 mg/kg/hr
- ICU sedation 1 mg kg/hr
- Anaesthesia 1-3 mg/kg IV, up to 10 mg/kg IM

Toxicity
Repetitive administration may induce damage to internal organs

In the central nervous system, psychotropic or psychedelic phenomena have been reported, including nightmares, hallucinations and dysphoria.

Ketamine may exert a direct negative inotropic effect and an indirect stimulatory effect on the cardiovascular system

Ketamine has been associated with elevated liver enzyme profile

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