TITLE: Ketamine for Adult Patients who Have Suffered Painful and Traumatic Injuries: A Review of Clinical Effectiveness, Cost-Effectiveness, Safety and Guidelines

DATE: 06 March 2014

CONTEXT AND POLICY ISSUES

Traumatic injury can result in pain that leads to subsequent activation of the sympathetic nervous system, suppression of humoral and cellular immune responses, a hypercoagulable state, and an increased risk of hyperglycemia.[1] If inadequately treated, the acute pain can potentiate the adverse effects of trauma,[2] resulting in respiratory, cardiovascular and hemodynamic instability.[1,3] Therefore, it is imperative that acute pain be treated[2] and an ideal analgesic agent should ameliorate pain without causing further instability.[4]

Ketamine, a non-competitive NMDA receptor antagonist, is a potent dissociative agent[5] used for its sedative, anesthetic, and analgesic properties.[6] First used clinically in the 1970 as an anesthetic, the use of low-dose ketamine in the pre-hospital setting is gaining favour as it possesses profound analgesic properties, while having the ability to preserve cardiovascular stability, spontaneous respiration, and protective airway reflexes.[6,7] These properties allow for the performance of painful procedures with minimal risk of complications.[8] Therefore, ketamine is an appealing agent for analgesia in traumatic injury,[9] and has been used as part of multimodal analgesia for acute and chronic pain.[10]

However, there are lingering concerns about the safety of ketamine in trauma patients, especially in those with traumatic brain or eye injuries. There have been concerns that ketamine can increase intracranial pressure (ICP), thereby having the potential to worsen traumatic brain injuries.[11] As a result, it has been historically contraindicated for use in patients with head injury.[5] However, more recent evidence surrounding ketamine's impact on ICP has been mixed,[12] with some studies suggesting no association between ketamine and increased ICP.[5] Ketamine also stimulates ciliary blood flow and as a consequence, concerns have been raised over its potential to increase intraocular pressure and worsen traumatic eye injuries.[13] It is unknown whether these concerns regarding ketamine extend to use in analgesia, where administered doses are generally lower than those used in anesthesia and sedation.[6]

This report will review the evidence surrounding the clinical effectiveness, safety, and cost-effectiveness of ketamine and guidelines for its use in adult patients who have suffered painful and traumatic brain or eye injury. This report will also review the evidence around the optimal dose of ketamine and its safety in adults with moderate to severe pain from traumatic injury who are conscious, and the comparative safety of ketamine against fentanyl and morphine in this population.

RESEARCH QUESTIONS

1. What are the clinical effectiveness and safety issues of ketamine for adult patients who have suffered painful and traumatic brain or eye injury?

2. What is the optimal dose of ketamine (IV, IM, and intranasally) and the safety surrounding its use at this dose in adults with moderate to severe pain from traumatic injury who are conscious?

3. What are the safety issues regarding the use of ketamine at low doses when compared to fentanyl and morphine for adults with moderate to severe pain from traumatic injury?

4. What is the cost-effectiveness of using ketamine for adult patients who have suffered painful and traumatic brain or eye injury?

5. What are the guidelines associated with the use of ketamine for adult patients who have suffered painful and traumatic brain or eye injury?

KEY FINDINGS

One study failed to show a difference between ketamine and morphine for analgesic effect in a post hoc analysis of a subset of patients with head trauma. No published trials were identified examining the clinical effectiveness and safety of ketamine in adult patients who have suffered painful and traumatic eye injury. No published trials were identified examining the optimal dose of ketamine in adults with moderate to severe pain from traumatic injury who are conscious. No published trials were identified examining the safety of low dose ketamine as compared to fentanyl and morphine for adults with moderate to severe pain from traumatic injury. No economic evaluations or evidence-based guidelines regarding the use of ketamine in adult patients who have suffered painful and traumatic brain and eye injuries were identified.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the adult population. The search was also limited to English language documents published between January 1, 2009 and February 6, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, and evaluated the full-text publications for final article selection, according to the selection criteria presented in Table 1:

Table 1: Selection Criteria

Population	Q1, 4, 5: Adults ≥18 year of age who have suffered painful and traumatic brain injury (TBI) or traumatic eye injury Q2 and 3: All patients experiencing moderate to severe pain from traumatic injury.
Intervention	Ketamine
Comparator	Opioid and non-opioid analgesic agents
Outcomes	Clinical effectiveness Safety Cost-effectiveness Guidelines
Study Designs	Health technology assessment, systematic review, meta-analysis, randomized controlled trials, non-randomized studies, economic evaluations, guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria.

Critical Appraisal of Individual Studies

Randomized controlled trials were assessed using the Scottish Intercollegiate Guidelines Network, Methodology checklist 2 (SIGN 50 Checklist 2).[14] A numeric score was not calculated for each study. Instead, the strengths and weaknesses of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 443 citations. Upon screening titles and abstracts, 420 citations were excluded, and 23 potentially relevant articles were retrieved for full-text review. In addition, 21 potentially relevant reports were retrieved by grey literature search. Therefore, a total of 44 potentially relevant reports were retrieved for full text review. Of the 44 reports, 43 did not meet the inclusion criteria. One report[4] was included in this review. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1). The one study was an RCT to assess the clinical efficacy and safety of ketamine versus morphine in trauma patients that included a subset of patients with head trauma. No studies were identified to assess the clinical efficacy and safety of ketamine in

patients with traumatic eye injury or evaluating the optimal dose and safety of ketamine in conscious patients with moderate to severe pain from traumatic injury. No studies were identified assessing the safety of low dose ketamine compared to morphine or fentanyl in patients with moderate to severe pain from traumatic injury. No studies evaluating cost-effectiveness or guidelines regarding the use of ketamine in adult patients who have suffered painful and traumatic brain or eye injury were identified.

Summary of Study Characteristics

1. *What are the clinical effectiveness and safety issues of ketamine for adult patients who have suffered painful and traumatic brain or eye injury?*

One RCT[4] was identified examining the clinical effectiveness and safety issues of ketamine for adult patients who have suffered painful and traumatic brain injury. The identified RCT was a prospective, cluster-randomized, non-blinded study conducted in the Quang Tri Province in Vietnam from September 2007 to March 2009. Trauma patients (n=312) in need of analgesia were treated by first responders in-field (i.e., prehospital at the site of the trauma) with either ketamine 0.2-0.3mg/kg through slow intermittent intravenous injections or a single morphine intramuscular injection of 10mg for adults or 5mg for children. The Quang Tri Province was divided equally into two, and analgesia treatment was alternated systematically at one month periods between the two geographical groups for the study duration. The main outcome of interest was change in pain rating using a Visual Analogue Scale (VAS) recorded by the same doctor at first in-field encounter and on hospital admission. Other outcomes included: events of agitation, vomiting and excessive salivation; and changes in respiratory rate, blood pressure, and level of consciousness. A subset of patients with head trauma was analyzed separately as a post hoc analysis.

Mean ketamine dose used in the study was 15mg, with 75% of patients requiring a single dose of medication. In the subset of patients with head trauma (n=57), the mean age was 34 years, and mean injury severity score (ISS) was 4.4 in the ketamine group (n=28) and 3.4 in the morphine group (n=29), which corresponds to injury severity of moderate and minor, respectively.[15] The mean time from injury to first in-field contact was 59 minutes and 55 minutes in the ketamine and morphine groups, respectively. Specific demographic information for this subset was unavailable, but the majority of patients enrolled in this study were male (77%) and older than 15 years in age (92.2%).

No evidence was identified regarding the clinical effectiveness and safety issues of ketamine for adult patients who have suffered painful and traumatic eye injury.

2. *What is the optimal dose of ketamine (IV, IM, and intranasally) and the safety surrounding its use at this dose in adults with moderate to severe pain from traumatic injury who are conscious?*

No evidence was identified examining the optimal dose of ketamine, and the safety surrounding the use of this dose in adults with moderate to severe pain from traumatic injury who are conscious.

3. *What are the safety issues regarding the use of ketamine at low doses when compared to fentanyl and morphine for adults with moderate to severe pain from traumatic injury?*

No evidence was identified examining the safety issues regarding the use of ketamine at low doses when compared to fentanyl and morphine for adults with moderate to severe pain from traumatic injury.

4. *What is the cost-effectiveness of using ketamine for adult patients who have suffered painful and traumatic brain or eye injury?*

No evidence was identified examining the cost-effectiveness of using ketamine for adult patients who have suffered painful and traumatic brain or eye injury.

5. *What are the guidelines associated with the use of ketamine for adult patients who have suffered painful and traumatic brain or eye injury?*

No guidelines regarding the use of ketamine for adult patients who have suffered painful and traumatic brain or eye injury were identified.

Summary of Critical Appraisal

The methodological quality of the identified RCT was considered poor as allocation concealment was unclear and there was no blinding of patients or doctors. Strengths of this study include a clearly defined research question, clearly described intervention and comparators, comparable baseline characteristics between the two groups, low drop-out rate; and inclusion of important outcomes of interest (e.g., change in clinician-rated VAS rating, adverse events).

Limitations of the identified RCT include its open-label design, lack of patient-rated pain outcomes, low inter-rater agreement between in-field doctors and hospital staff for the clinician-rated VAS rating, and lack of long-term follow-up. Limitations of this study more specific to patients with head trauma include small sample size, no measurement of intracranial pressure (ICP), and the post hoc nature of the analysis. No sensitivity analysis data was presented examining the effect of risk variables on the primary outcome. Moreover, there is limited generalizability of the study results as it was conducted at a single centre in rural Vietnam.

Summary of Findings

1. *What are the clinical effectiveness and safety issues of ketamine for adult patients who have suffered painful and traumatic brain or eye injury?*

With respect to the clinical effectiveness and safety issues of ketamine for adult patients who have suffered painful and traumatic brain injury, one RCT[4] was available as evidence. In a post hoc analysis of the subset of patients with head trauma, ketamine failed to show a difference when compared to morphine for the outcome of change in clinician-rated VAS rating, with a mean change on the VAS score of 2.9 points (95% confidence interval [CI] -0.9 to 1.1) in both groups. A similar number of patients in each group maintained the same level of consciousness on hospital admission as in-field (27/28 ketamine patients vs. 26/29 morphine patients). No specific safety data was provided for the subset of patients with head injury. In the overall RCT, more nausea and vomiting was seen in the morphine group [14% difference (95% CI 8% to 22%)], and more agitation was seen in the ketamine group [9.5% difference (95% CI 4% to 16%)]. No differences were seen between the two groups with respect to changes in blood pressure and respiratory rate.

No information was available regarding the clinical effectiveness and safety issues of ketamine for adult patients who have suffered painful and traumatic eye injury.

2. *What is the optimal dose of ketamine (IV, IM, and intranasally) and the safety surrounding its use at this dose in adults with moderate to severe pain from traumatic injury who are conscious?*

No information on the optimal dose of ketamine and the safety surrounding its use in adults with moderate to severe pain from traumatic injury who are conscious was identified.

3. *What are the safety issues regarding the use of ketamine at low doses when compared to fentanyl and morphine for adults with moderate to severe pain from traumatic injury?*

No information on the safety issues regarding the use of ketamine at low doses when compared to fentanyl and morphine for adults with moderate to severe pain from traumatic injury was identified.

4. *What is the cost-effectiveness of using ketamine for adult patients who have suffered painful and traumatic brain and eye injuries?*

No information on the cost-effectiveness of using ketamine for adult patients who have suffered painful and traumatic brain or eye injury was identified.

5. *What are the guidelines associated with the use of ketamine for adult patients who have suffered painful and traumatic brain or eye injury?*

No evidence-based guidelines regarding the use of ketamine for adult patients who have suffered painful and traumatic brain or eye injury were identified.

Limitations

There is a lack of high quality evidence to support the use of ketamine monotherapy in adult patients with painful traumatic brain injury. There was a lack of blinding, allocation concealment, and long-term follow-up in the identified RCT. Moreover, sample size was small and analysis was done post hoc for the subset of patients with head trauma. Pain was measured by care providers, but no pain rating was performed by the patients, which may lead to inaccuracies in ratings for a subjective outcome such as pain. The RCT population included both children and adults, and the number of children in the subset of patients with head trauma is unknown. Therefore, the findings may not be entirely generalizable to either group. No information was available regarding effects on intracranial pressure. There is limited generalizability of available results from the RCT as it was conducted at a single centre in rural Vietnam.

No studies or information was identified for patients with traumatic eye injury, the optimal dose and safety of ketamine in adults with moderate to severe pain from traumatic injury who are conscious, and the safety of ketamine compared to fentanyl and morphine in adults with moderate to severe pain from traumatic injury. No economic evaluations and evidence-based guidelines were identified for use of ketamine in patients with painful and traumatic brain or eye injury.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited evidence is available to compare the effectiveness and safety of ketamine to morphine in patients with head trauma. In a post hoc analysis of a subset of patients with head trauma, investigators failed to show a difference between ketamine and morphine, with a similar number of patients in both groups maintaining the same level of consciousness. No evidence is available to compare ketamine to other analgesic agents in patients with traumatic brain injury. No information on the effectiveness and safety of ketamine for analgesia in patients with traumatic eye injury was identified. No information on the optimal dose of ketamine and the safety surrounding its use in adults with moderate to severe pain from traumatic injury who are conscious was identified. No information on the safety issues regarding the use of ketamine at low doses when compared to fentanyl and morphine for adults with moderate to severe pain from traumatic injury was identified. No economic evaluations or evidence-based guidelines were identified. Therefore, no conclusions can be made for these research questions. Well-designed RCTs are needed to assess the clinical effectiveness and safety of ketamine as monotherapy for the indication of analgesia in patients who have suffered traumatic injury.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Keene D, Rea WE, Aldington D. Acute pain management in trauma. Trauma. 2011;13:167-79.

2. Cohen SP, Christo PJ, Moroz L. Pain management in trauma patients. Am J Phys Med Rehabil. 2004 Feb;83(2):142-61.

3. Sinha N, Cohen SP. Pain management for trauma. In: Vadivelu N, Urman RD, Hines RL, editors. Essentials of pain management. New York: Springer; 2011. p. 401-15. Chapter 19.

4. Tran KP, Nguyen Q, Truong XN, Le V, Le VP, Mai N, et al. A Comparison of ketamine and Morphine Analgesia in Prehospital Trauma Care: A Cluster Randomized Clinical Trial in Rural Quang Tri Province, Vietnam. Prehosp Emerg Care. 2014 Jan 8. Epub ahead of print.

5. Caricato A, Tersali A, Pitoni S, de WC, Sandroni C, Bocci MG, et al. Racemic ketamine in adult head injury patients: use in endotracheal suctioning. Crit Care. 2013 Nov 8;17(6):R267.

6. Cohen SP, Liao W, Gupta A, Plunkett A. Ketamine in pain management. Adv Psychosom Med. 2011;30:139-61.

7. Jolly T, McLean HS. Use of ketamine during procedural sedation: indications, controversies, and side effects. J Infus Nurs. 2012 Nov;35(6):377-82.

8. Jamal SM, Fathil SM, Nidzwani MM, Ismail AK, Yatim FM. Intravenous ketamine is as effective as midazolam/fentanyl for procedural sedation and analgesia in the emergency department. Med J Malaysia [Internet]. 2011 Aug [cited 2014 Feb 11];66(3):231-3. Available from: http://www.e-mjm.org/2011/v66n3/Intravenous_Ketamine.pdf

9. Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: a systematic review. Acta Anaesthesiol Scand. 2011 Jul;55(6):638-43.

10. Polomano RC, Buckenmaier CC, III, Kwon KH, Hanlon AL, Rupprecht C, Goldberg C, et al. Effects of low-dose IV ketamine on peripheral and central pain from major limb injuries sustained in combat. Pain Med. 2013 Jul;14(7):1088-100.

11. Hughes S. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 3: is ketamine a viable induction agent for the trauma patient with potential brain injury. Emerg Med J. 2011 Dec;28(12):1076-7.

12. Chang LC, Raty SR, Ortiz J, Bailard NS, Mathew SJ. The emerging use of ketamine for anesthesia and sedation in traumatic brain injuries. CNS Neurosci Ther. 2013 Jun;19(6):390-5.

13. Czarnik T, Gawda R, Kolodziej W, Latka D, Sznajd-Weron K, Weron R. Association between intracranial pressure, intraocular pressure and mean arterial pressure in patiens with traumatic and non-traumatic brain injuries. Injury [Internet]. 2009 [cited 2014 Feb

21];40:33-9. Available from: http://prac.im.pwr.wroc.pl/~hugo/publ/Czarnik_etal09_Injury.pdf

14. Scottish Intercollegiate Guidelines Network. Methodology checklist 2: randomized controlled trials [Internet]. In: SIGN 50: a guideline developer's handbook. Edinburgh: SIGN; 2008 [cited 2014 Jan 14]. Available from: http://www.sign.ac.uk/methodology/checklists/20121206_Checklist_for_controlled_trials.doc

15. Stevenson M, Segui-Gomez M, Lescohier I, Di SC, Donald-Smith G. An overview of the injury severity score and the new injury severity score. Inj Prev [Internet]. 2001 Mar [cited 2014 Feb 20];7(1):10-3. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1730702

APPENDIX 1: Selection of Included Studies