ACUTE PAIN SECTION

Review Article

A Systematic Review of Ketamine as an Analgesic Agent in Adult Burn Injuries

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Abstract

Objective. To assess the current literature regarding the effectiveness and side-effect profile of intravenous ketamine as a means of pain relief when compared with placebo or as an adjunct to opioid analgesia in patients exposed to burn injury.

Design. Electronic searches of MEDLINE, CINAHL, Embase, and The Cochrane Library databases from 1966 onward were used to identify clinical trials comparing ketamine with placebo in the adult burn population.

Outcomes Measured. Effectiveness and side-effect profile of ketamine as an analgesic agent in burn injuries.

Results. Four experimental trials involving 67 patients were identified. Due to heterogeneity of studies, pooling of the results and meta-analysis were not possible. Intravenous ketamine showed some efficacy as an analgesic for burn injuries, with a reduction in secondary hyperalgesia when compared with opioid analgesia alone. Combination therapy of ketamine and morphine resulted in the abolishment of windup pain phenomena. The side-effect profile did not result in the withdrawal of any participants included in the studies’ results.

Conclusions. Further well-designed randomized controlled trials conducted in burn-specific populations are warranted, thus enabling the development of a relevant evidence base to support its clinical use.

Key Words. Burns; Ketamine; Pain Management; Analgesia

Introduction

Burn injury, by damaging both superficial and deep tissues, creates multiple mechanisms for pain. Pain is therefore a common and distressing symptom for burn patients, and its management is of particular importance [1]. The mechanism for pain in burn injuries is due to inflammatory cascades and pathways that form part of the pathophysiological process following tissue and nerve injuries. Excess production of mediators, including calcitonin gene-related peptide and substance P, and activation of N-methyl-D-aspartate (NMDA) receptors can cause sensitization of A-delta and C sensory nerve fibers [2]. As a result of this process, patients experience pain at the injured area in the form of allodynia and hyperalgesia; the process can also cause pathological secondary hyperalgesia in surrounding uninjured tissues [3,4]. Repeated tissue trauma and painful stimuli, such as during frequent dressing changes and wound debridements, in conjunction with inflammatory processes and infection, can result in neuroplastic adaptations throughout the central nervous system, particularly hyperexcitability of the dorsal horn of the spinal cord [2]. Pain afferent sensory impulses undergo facilitation and amplification to a given stimulus, contributing to the generation and maintenance of chronic or persistent pain [4–6]. Furthermore, μ receptor activation by opioids, the mainstay of analgesia in burn patients, has been thought to increase...

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glutamate synaptic effectiveness at the level of NMDA receptors, thus inducing opioid tolerance and compounding management problems in the treatment of burn pain [7]. It is important that agents administered with the aim of minimizing pain be both effective as a form of analgesia and have minimal side effects.

Ketamine is an intravenous analgesic and anesthetic commonly used in burn patients [8], despite minimal clinical evidence of its efficacy. First pioneered in the 1960s in the United States, its main action is dissociative anesthesia. By acting at the level of NMDA receptors as a noncompetitive NMDA receptor antagonist, ketamine reduces the presynaptic release of glutamate in addition to complex interaction with opioid receptors. Ketamine is thus thought to both prevent the induction of central sensitization and windup, in particular as an antiallodynic and anti-hyperalgesic agent, as well as reduce the development and maintenance of opioid tolerance [9,10]. Ketamine administration can result in numerous side effects, secondary to the promotion of dissociation between thalamic function and the limbic system. These side effects have been documented in a dose-dependent fashion, including nausea and vomiting, hallucinations, mood alteration, bizarre dreams, and emergence delirium, all of which can persist for several weeks after administration [11,12]. However, ketamine has the distinct advantage over opioid analgesia in causing less respiratory depression and in preserving cardiovascular stability in patients.

Although there have been multiple studies discussing the use of ketamine as an intravenous anesthetic and analgesic in acute pain, particularly in a postoperative setting [10,13], there have been no comprehensive review articles discussing its specific utility in burn patients. The purpose of this review is to assess the current literature regarding the effectiveness and side-effect profile of intravenous ketamine as a means of pain relief when compared with placebo or as an adjunct to opioid analgesia in patients exposed to burn injury.

Methods

Data Sources and Search Strategy

A structured literature search was performed in MEDLINE, Embase, and The Cochrane Library from 1966 onward using the key words related to “burns” and “thermal injury” with generic and trade name derivatives such as “ketamine” and “ketelar.” In addition to the automated search strategies, reference lists of related journal articles, key journals, and existing reviews were hand searched for additional trials. Two researchers (LH, JW) independently conducted the literature search. All searches were limited to articles in English [14].

Study Selection Criteria and Procedures

The abstracts retrieved through the search were checked by applying the eligibility criteria, which examined the efficacy of intravenous ketamine in any dose as a means of pain relief in adult patients exposed to burn injury regardless of etiology. In this instance, we defined low-dose ketamine as less than 0.15 mg/kg/h and intermediate-dose ketamine as greater than 0.3 mg/kg/h. Patients were to have received ketamine or placebo, or both ketamine and basic analgesics (e.g., morphine) or basic analgesics alone. We included studies irrespective of the type of intervention, setting, or phase of burn care. Systematic or narrative reviews, case reports, economic evaluations, and studies that used a pediatric population, or did not present appropriate information for data extraction, were excluded.

Data Analysis and Synthesis

A narrative approach was adopted in order to synthesize the findings of the included studies. Due to the heterogeneity of studies, data could not be pooled using meta-analytical methods and were thus described individually. Limited reporting of data precluded the calculation of effect sizes. Risk of bias for each study was assessed according to the recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions [14] and can be found in Table 1.

Results

The search strategy identified 554 studies for potential inclusion. Independent scrutiny of the titles and abstracts identified 21 potentially relevant articles. We excluded 15 because they were a mixture of studies that looked at sedation alone, had no control, or were either narrative reviews or other descriptive articles. Two further were excluded as they looked at routes of administration of ketamine other than intravenous. The remaining four studies [15–18] formed the basis of this review, the characteristics of which are provided in Table 2.

Description of RCTs

The included trials were published between 1996 and 2004 included data on 106 participants, all of which received ketamine and control therapies on alternate testing days. One of the four studies [18] had three study arms. The naloxone arm in this study was excluded from systematic review.

Ketamine doses ranged between regimes used and were reported in milligram per kilogram [16], milligram per kilogram per hour [15,17] or microgram per kilogram per minute [18]. In two studies, ketamine was administered as a stat dose or bolused over 15 minutes, followed by a continuous intravenous infusion for 30 or 150 minutes [15,17]. In the remaining studies, the infusion was commenced 0 or 50 minutes after thermal injury and was continued anywhere from 10 to 75 minutes [16,18].

All studies included healthy volunteers with an induced burn from a controlled laboratory heat injury. There were no trials conducted in a clinical capacity on burn inpatients. All of the thermal injuries were induced on the
medial/lateral surface of the right/left calf by a standard thermode strapped to the skin. The standard thermode (Thermotest, Somedic A/B, Solentuna, Sweden) used in all cases was $25 \times 50$ mm in size. Temperature of the thermode varied from 46 to 47°C with a heat time of 7 minutes on the skin. The thermode was applied to the skin with a weight of 250 g or 4.5 kPa [15,18], with view to producing an injury-graded first to mild second-degree burn. All participants underwent education to familiarize them with the proposed burn injury and measurement procedures on a separate day. Individual burn injuries were separated over a number of days, with a new burn injury induced on each of the study days to test the various arms of the analgesic regimes i.e., 3 days [16] with a minimum of 4 days [16] between testing.

A wide variety of outcomes were examined. Not all studies reported the same end points. Primary hyperalgesia was measured using a thermode, and visual analog scales (VAS) was used by patients to rate pain intensity. Three studies measured both thermal and tactile thresholds, as well as heat pain detection thresholds, defined as the lowest temperature perceived as painful from baseline [15–17]. One study measured tactile thresholds only [18]. All studies examined tactile stimulation by pinpricking the site using the von Frey technique. Secondary outcome measures included mechanical hyperalgesia, as brush or punctate stimulation, in the area of secondary hyperalgesia, and the side-effect profile of each treatment arm.

**Effect of the Intervention**

Although the four studies included in this review used similar outcome measures, significant reported shortcomings were identified, so any analysis of pooled data applying statistical methods was not possible or appropriate. The review authors analyzed all results reported below.

**Effectiveness of Ketamine as a Form of Primary Analgesia for Thermal Injuries**

Ketamine intravenous infusions at intermediate doses (0.3 mg/kg/h) showed a statistically significant reduction in primary hyperalgesia at the site of the burn injury when compared with low-dose ketamine (0.15 mg/kg/h) or placebo [15]. Regimes involving both bolus then intravenous ketamine and continuous intermediate-dose intravenous ketamine showed significant reduction in both secondary punctuate and brush hyperalgesia ($P < 0.04$ and $P < 0.002$, respectively) when compared with placebo [15]. Continuous low-dose ketamine infusion was effective in reducing secondary brush hyperalgesia only ($P < 0.03$) [15]. The peak reduction in mechanical stimulus secondary hyperalgesia (to both punctuate and brush) was demonstrated to be statistically significantly lower at 15 minutes’ postadministration of intravenous ketamine than with placebo; however, hyperalgesia gradually returned between 45 and 75 minutes’ postadministration of intravenous ketamine in this particular study [16].

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**Table 1**

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Risk of bias assessment</th>
<th>Other Bias</th>
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<tbody>
<tr>
<td>Ilkjaer et al.</td>
<td>Low risk: all prespecified outcomes reported</td>
<td>Low risk</td>
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<tr>
<td>Warncke et al.</td>
<td>Low risk: low risk: all prespecified outcomes reported</td>
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<tr>
<td>Mikkelsen et al.</td>
<td>Low risk: low risk: all prespecified outcomes reported</td>
<td>Low risk</td>
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<tr>
<td>Shulte et al.</td>
<td>Low risk: low risk: all prespecified outcomes reported</td>
<td>Low risk</td>
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| Ilkjaer et al.  | Denmark     | 19 healthy volunteers | 1. 0.15 mg/kg ketamine + 0.15 mg/kg/h ketamine  
2. 0.3 mg/kg ketamine + 0.3 mg/kg/h ketamine                  | Placebo + placebo         | Bolus dose followed by continuous infusion                                   | Primary hyperalgesia  
Secondary hyperalgesia  
Side effects:  
- Sedation  
- Discomfort  
- Hallucinations  
- Other sensations |
| Warncke et al.  | Norway      | 12 healthy volunteers | 1. 0.15 mg/kg ketamine  
2. 0.15 mg/kg morphine                                                      | Placebo                  | Intravenous           | Primary hyperalgesia  
Secondary hyperalgesia:  
Side effects:  
- Fatigue  
- Dizziness  
- Visual disturbances  
- Nausea  
- Paresthesia  
- Feeling of unreality  
- Feeling of muscular stiffness  
- Sleepy  
- Pleasant feeling |
| Mikkelsen et al.| Denmark     | 25 healthy volunteers (2 excluded) | 1. 0.8 mg/15 min, followed by 0.4 mg/h naloxone + 0.3 mg/kg/15 min, followed by 0.3 mg/kg/h ketamine  
2. Placebo + 0.3 mg/kg/15 min, followed by 0.3 mg/kg/h ketamine | Placebo + placebo         | Intravenous infusion      | Primary hyperalgesia  
Secondary hyperalgesia  
Side effects:  
- Sedation  
- Nausea  
- Hallucinations |
| Schulte et al.  | Sweden      | 11 healthy volunteers | 1. 9 µg/kg/min ketamine  
2. 10 µg/kg/min morphine  
3. 9 µg/kg/min ketamine + 10 µg/kg/min morphine | Placebo                  | Intravenous infusion      | Primary hyperalgesia  
Secondary hyperalgesia  
Side effects:  
- Headache  
- Nausea/vomiting  
- Flush  
- Chest oppression  
- Tiredness  
- Dizziness  
- Anxiety  
- Out-of-body sensation |
No enhanced analgesic effect was seen when morphine was administered concurrently with ketamine with regard to secondary hyperalgesia and pain thresholds [18]. However, windup-like pain (pain on repetitive stimulation) was nearly abolished with combined morphine and ketamine administration, and lasted for the duration of the experimental session (~75 minutes) in the area of secondary hyperalgesia [18]. The effect was more short-lived in the area of primary hyperalgesia, lasting only 15 minutes post infusion initiation [18].

**Side Effects of Ketamine Use**

Overall, the side effects of ketamine in all but one patient were described as weak to moderate, and none were substantial enough to result in patient withdrawal from the studies. Nausea and vomiting were noted to increase when ketamine was used in combination with morphine compared with either agent used independently or placebo [18]. Sedation was much more common in the ketamine arms than in the placebo arms of all studies, as would be expected; drowsiness was described in a dose-dependent fashion [15].

Discomfort at the injection site occurred more frequently following bolus administration of high-dose intravenous ketamine, in contrast to low dose, and was more pronounced immediately after bolus intravenous injections and with high-dose ketamine infusions, but was noted to substantially decline or disappear during continuous infusions of high-dose intravenous ketamine. There were no reports of discomfort with low-dose intravenous ketamine infusion [15].

No hallucinations were described in any of the study groups, although some participants did experience sensations such as “feeling drunk,” “dizziness,” or changed perceptions of body parts while receiving ketamine intravenously [15–17].

**Discussion**

The goal of this systematic review was to examine the effectiveness and side-effect profile of intravenous ketamine as a means of pain relief when compared with placebo or as an adjunct to opioid analgesia in patients exposed to burn injury. We found four RCTs meeting the predetermined criteria that tested the efficacy of ketamine as an analgesic agent against a placebo control. Ketamine used intravenously was shown to reduce secondary hyperalgesia when compared with placebo in all studies evaluated [15–18]. This was in keeping with its common clinical use as an anesthetic agent in children with burns and scalds; they found ketamine to be a safe, effective, and convenient anesthetic, with minimal unpleasant side effects [22].

More specific to this systematic review, the long-term use of ketamine as a sedation agent and analgesic was described in a single case report of a patient with severe head and neck burns where an intravenous ketamine infusion was shown to reduce opioid requirements, opiate-related side effects, and improve pain control [24]. A recent prospective study by MacPherson et al. investigated the use of a combination of ketamine/midazolam patient-controlled analgesia (PCA) for burn dressing changes at a programmed bolus dose of ketamine 20 mg/midazolam 0.5 mg intravenously. The authors concluded the use of ketamine in the form of intravenous PCA to be effective as an analgesic regime for burns dressing changes [8].

In the pediatric population, ketamine was shown to be an effective agent in a clinical setting for sedation during painful procedures at the bedside when administered intravenously [25]. Another pediatric study suggested oral...
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ketamine improved analgesia and sedation in facilitating wound care procedures among pediatric burn patients [26]. A pediatric case study looked at long-term (>30 days) morphine and ketamine infusions in a 14-month-old child; they showed the plasma clearance of ketamine to be 32 mL/min/kg, greater than previously reported in older children and adults. This study noted no complications despite the high-dose long-term therapy [27]. Intravenous ketamine was infused for 37 days in a 9-year-old child with 42% total body surface area burns, without demonstrated tolerance or psychomimetic side effects. Rapid weaning of the infusion was achieved without any evidence of withdrawal [28].

Although ketamine has been associated with psychomimetic side effects such as hallucinations and nightmares [8,13,29], these side effects were not demonstrated by the route of administration when using subanesthetic doses of ketamine for analgesic effects. It must be noted that one study withdrew a participant for psychomimetic effects during infusion [17]; no other information regarding this exclusion was reported. Other side effects were noted to be present in a dose-related manner [15]. A recent prospective study by Newton et al. evaluated the use of intravenous ketamine for procedural sedation in adult patients [30]. In this study, eligible patients received an initial dose of ketamine 0.5 mg/kg intravenously, which was repeated 5 minutes after if adequate sedation had not been achieved. Adequate sedation was achieved in 91 of 92 patients, however twenty of the 92 patients experienced adverse events, 12 of which were emergence-related reactions. It should be noted that the doses used in the study by Newton and Fitton administered for sedation tended to be higher than those analgesic doses used in the included RCTs for this review.

The systematic review was limited by the methodological weaknesses of the original studies and the variability of the study settings. The included studies were experimental in nature, with volunteers sustaining superficial burns in a controlled environment. This did not accurately reflect the clinical potential for ketamine as an analgesic, particularly in large burn centers where injuries are frequently more extensive and complex. More so, these injuries are usually nonvoluntary, where the patient’s perception of pain is often multifaceted and involves several pain outcome domains such as emotional function, physical functioning, and patient assessment and satisfaction with treatment. These domains require complex assessment tools to adequately measure the multiple domains that affect the pain experience in burn patients. Given the voluntary nature of the participants in the included studies, the clinical relevance of these results should be interpreted cautiously.

The patients within each experimental group in the included studies had burns encompassing a relatively small surface area. There is little literature describing the effect of burn size on the type or intensity of pain that will develop in burn patients. Furthermore, preexisting and premorbid participant factors were not explored in depth in the included studies, which may have impacted on the participants’ perceptions of pain. This reinforced the need for randomized trials using appropriate multidimensional pain assessment tools in a clinical context to adequately assess the use of ketamine as an analgesic agent in burn patients.

Furthermore, all included studies contained small sample sizes, the result of which may be that they were unable to show clinically significant results that might be discovered by repeating the experiments with larger participant populations. The crossover period between testing was a minimum of 4 days; although the half-life of ketamine is reportedly 2–4 hours, the systemic analgesic or antihyperalgesic effects of ketamine may last beyond this time frame and thus must be interpreted accordingly. The exact mixture of ketamine infused (s-ketamine vs racemic) was not reported in the studies. Additionally, the short-term duration over which all studies were conducted did not allow analysis of the effect of ongoing repeated doses nor take into consideration the side effects of prolonged use.

Further limitations existed in that we were restricted to electronic databases, which may not have been representative of all indexed studies. Other medical databases, burn- and pain-specific texts, conference proceedings, national registries, and nonpublished RCTs were not systematically searched. In those studies that were identified by our electronic search, limitations existed with respect to the reportable outcomes of the studies and how these were presented. Three articles report only P values with descriptive analysis and no actual VAS figures, with only two articles including mean and standard deviations for further analysis. As a result, further assessment and pooling of data for the purposes of this review was not possible given the differences in study designs available for comparison. Thus, our ability to draw either positive or negative conclusions as to the definitive use for ketamine as an analgesic agent was extremely limited.

Conclusion

Although intravenous ketamine is frequently used in practice as an analgesic in burn injuries, on the basis of the data from this systematic review, there appears to be insufficient evidence to make definitive recommendations for its use. On the basis of the little data extractable from the included studies, intravenous ketamine appears to warrant investigation as an analgesic in burn injuries. Further well-designed RCTs conducted in burn-specific populations are warranted, thus enabling the development of a relevant evidence base to support its clinical use.

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References


