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Ketamine in the Management of Acute Pain in Burned Patients: A Systematic Review / Ketamina en el Manejo del Dolor Agudo en Pacientes Quemados: Revisión Sistemática

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ABSTRACT

Introduction: the management of acute pain in patients with burns is a significant challenge due to the intensity of these injuries and their physiological impact. Ketamine, an NMDA receptor antagonist, has emerged as a promising analgesic option thanks to its ability to modulate hyperalgesia and reduce opioid dependence.
Objective: evaluate the benefits and risks associated with the use of ketamine in burn patients.
Method: a systematic search was conducted in PubMed, Embase, Cochrane Library, and Google Scholar to identify studies published in the corresponding period between 2010 and 2023. Inclusion criteria considered randomized controlled trials (RCTs), meta-analyses, and systematic reviews evaluating the use of ketamine as primary or adjuvant treatment in patients with burns. Analgesic efficacy and reported adverse effects were analyzed.
Results: nine studies were included in the analysis, highlighting the effectiveness of ketamine in reducing acute pain and decreasing opioid consumption. Combined ketamine-opioid regimens demonstrated superior outcomes compared to opioids alone. The most common adverse effects were mild and transient, mainly psychomimetic symptoms, which did not affect treatment continuity. Sustained use of ketamine has been linked to the development of tolerance and risk of dependence.
Conclusions: ketamine represents an effective and safe option for the management of acute pain in burn patients. However, further randomized and larger clinical trials are needed to standardize doses and establish more effective clinical guidelines tailored to the needs of these patients.

Keywords: Ketamine; Burns; Acute Pain; Pain Management; Analgesics.

RESUMEN

Introducción: el manejo del dolor agudo en pacientes con quemaduras es un reto significativo debido a la intensidad de estas lesiones y su impacto fisiológico. La ketamina, un antagonista de los receptores NMDA, ha emergido como una opción analgésica prometedora gracias a su capacidad para modular la hiperalgesia y reducir la dependencia de opioides.
Objetivo: evaluar los beneficios y riesgos asociados al uso de ketamina en pacientes quemados.
Método: se llevó a cabo una búsqueda sistemática en PubMed, Embase, Cochrane Library y Google Scholar para identificar estudios publicados en el período correspondiente entre 2010 hasta 2023. Los criterios de inclusión consideraron ensayos clínicos controlados aleatorizados (ECA), metaanálisis, y revisiones sistemáticas que evaluaran el uso de ketamina como tratamiento principal o adyuvante en pacientes con quemaduras. Se analizaron la eficacia analgésica y los efectos adversos reportados.
Resultados: se incluyeron nueve estudios en el análisis, destacando la efectividad de la ketamina

en la reducción del dolor agudo y la disminución del consumo de opioides. Los regímenes combinados de ketamina y opioides demostraron resultados superiores en comparación con los opioides solos. Los efectos adversos más comunes fueron leves y transitorios, principalmente síntomas psicomiméticos, que no afectaron la continuidad del tratamiento. El uso sostenido de ketamina se ha vinculado con el desarrollo de tolerancia y riesgo de dependencia.
Conclusiones: la ketamina representa una opción eficaz y segura para el manejo del dolor agudo en pacientes con quemaduras. Sin embargo, se necesitan más ensayos clínicos aleatorizados y de mayor escala para estandarizar las dosis y establecer guías clínicas más efectivas y adaptadas a las necesidades de estos pacientes.

Palabras clave: Ketamine; Burns; Acute Pain; Pain Management; Analgesics.

INTRODUCTION

The management of acute pain in burn patients remains a complex clinical challenge due to the severity of the injuries, the activation of intense inflammatory responses, and the sensitization of N-methyl-D-aspartate (NMDA) receptors. These mechanisms contribute not only to significant hyperalgesia but also, in many cases, to the development of persistent pain that can profoundly affect the patient's recovery and quality of life. Burns are skin injuries resulting from exposure to heat, chemicals, electricity, or radiation. They are classified into different degrees according to the depth and damage caused to the tissues:

- First degree: affects only the epidermis. They are characterized by redness, pain, and dryness, without blistering. They are common in sunburns.
- Superficial second degree: these involve the epidermis and the upper part of the dermis. They present with blisters, moist skin, and intense pain. This type of burn usually heals in a couple of weeks.
- Deep second degree: affects the deeper layers of the dermis. Blisters may be present, but there is a greater risk of scarring. Pain perception may be reduced due to damage to the nerve endings.
- Third-degree: burns involve all layers of the skin, reaching the subcutaneous tissue. They are characterized by charred or whitish skin and are often accompanied by a loss of sensation in the affected area, as nerve endings are destroyed.

Burns, by compromising both superficial and deep tissues, trigger a series of pathophysiological responses that intensify pain perception. This symptom is undoubtedly one of the most distressing and prevalent in affected patients, representing a priority clinical challenge. The pain associated with burns extends beyond the initial damage to the skin and underlying tissues.

Tissues, but it is also mediated by complex inflammatory and neuropathological processes. Factors such as the release of inflammatory mediators (CGRP and substance P) and the activation of NMDA receptors play a key role in sensitizing A-delta and C nerve fibers, which transmit pain signals.[1]

As a result, patients experience symptoms such as allodynia (pain in response to normally non-painful stimuli) and hyperalgesia (exaggerated pain response to typically moderate stimuli).[2,3] In addition, routine procedures in burn management, such as frequent dressing changes and wound debridement, can lead to neuroplastic adaptations in the central nervous system, particularly in the posterior spinal cord. These adaptations amplify pain-related nerve impulses,

contributing to the development of chronic pain.[4,5,6]

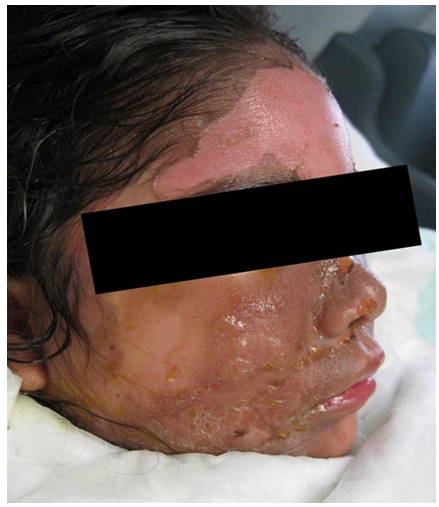

Figure 1. Partial-thickness burn showing blisters and redness. Image provided by Steven E Wolf, MD

On the other hand, although opioids are considered the mainstay of analgesic treatment in these patients, their prolonged use can increase the synaptic effectiveness of glutamate in receptors.

In this context, ketamine, a non-competitive antagonist of NMDA receptors, has gained ground as a valuable option for the management of acute pain in burns. Although its official indication by the Spanish Agency for Medicines and Health Products (AEMPS) is as a general anesthetic in surgical procedures, its analgesic effect has been widely documented, especially in painful procedures such as debridement and skin grafting.

Pharmacologically, ketamine is mainly administered intravenously (IV), although in specific contexts it can also be used intramuscularly (IM). Intravenous analgesic doses are usually between 0,1 and 0,5 mg/kg. In comparison, anesthetic doses can reach 1-2 mg/kg in an intravenous bolus, followed by a continuous infusion adjusted to the patient's needs. The analgesic effect of ketamine lasts an average of 30 to 60 minutes, making it a handy tool in brief but intensely painful procedures, such as minor surgery or wound care.[7]

However, prolonged use of ketamine has its limitations, mainly due to its potential for abuse, dependence, and adverse neuropsychiatric effects. In addition, its combination with opioids can increase sedative and psychomimetic effects, requiring careful monitoring by the medical team.

In terms of its application based on the severity of burns, ketamine is mainly used in deep second-degree and third-degree burns, where damage to tissues and peripheral nerves causes high-intensity pain. More superficial burns, such as first-degree burns, usually respond adequately to conventional analgesics.

The administration of ketamine is especially relevant in deep burns, both in the management of acute pain and during invasive procedures.

Finally, this systematic review seeks to answer the following key question: What are the benefits and risks of using ketamine, either as monotherapy or in combination with other drugs, in patients with burns?

Through a detailed analysis of the current literature, we aim to address this question and provide a solid basis for the development of more effective clinical guidelines that are tailored to the needs of these patients.

METHOD

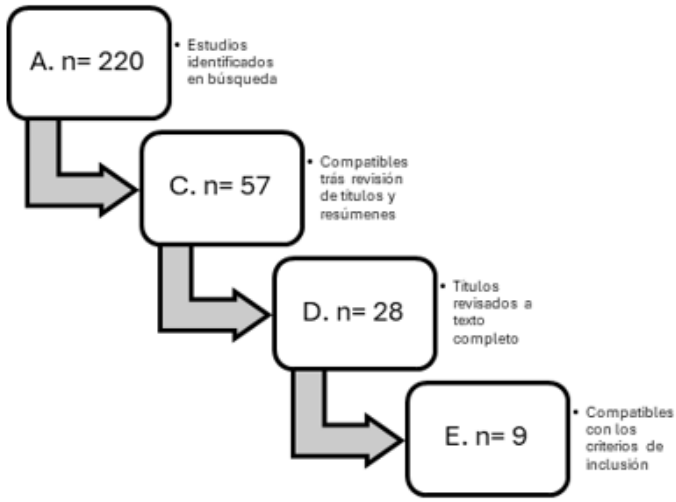

Figure 2. PRISMA Flowchart

Articles for this review were selected through a systematic search of several scientific databases, including PubMed, Embase, Cochrane Library, and Google Scholar. A combination of MeSH terms and keywords related to the review topic was used to identify relevant studies. The search was conducted between January 2010 and December 2023, and studies were filtered according to pre-established inclusion criteria.

The MeSH terms used in the search were:

- Ketamine.
- Burns.
- Acute Pain.
- Pain Management.
- Analgesics.

These terms were combined using Boolean operators: AND to incorporate key terms and OR to include synonyms or related terms.

Initial searches of titles and abstracts were conducted, followed by a detailed review of selected articles. Studies that met the inclusion criteria were downloaded and analyzed in their entirety. Those that did not meet the established criteria or lacked the necessary information were discarded.

Study Design

This systematic review adopted quantitative variables to examine and analyze the available literature on the use of ketamine in the management of acute pain in patients with severe burns. Studies of various designs were included, such as randomized controlled trials (RCTs), meta-analyses, and systematic reviews. The objective of this review was to evaluate the benefits of using ketamine, both as monotherapy and in combination with other drugs, and to analyze its possible adverse effects.

Study Population

The population of interest in this review consisted of publications of studies conducted in adult patients who suffered severe burns and received analgesic treatment. Studies addressing the use of ketamine at any stage of pain treatment were included, whether in acute management in the emergency setting or during postoperative treatment in burn units.

Inclusion Criteria

- Publications of studies that included Adult patients with deep second-degree and third-degree burns requiring analgesic treatment.
- Studies that used ketamine for acute pain management, either as monotherapy or in combination with other analgesic drugs.
- Randomized controlled trials (RCTs), meta-analyses, and reviews that included burn patients and reported data on the use of ketamine.
- Articles in English, Spanish, or Portuguese published between 2010 and 2023.

Exclusion criteria

- Preclinical studies
- Studies conducted in patients with a confirmed diagnosis of cancer.
- Studies that included patients undergoing chemotherapy or radiotherapy during the management of acute pain.

Scope of the study

The study was conducted at the Inter-American Open University using bibliographic resources accessible in the academic environment.

RESULTS

Analgesic effect and reduction in opioid consumptionKetamine is an effective analgesic in various burn pain treatment scenarios, especially when administered together with opioids or other adjuvant agents.

In clinical studies, the combination of ketamine, tramadol, and dexmedetomidine significantly reduced post-procedure pain ($p < 0,05$). According to the VAS scale, pain reduction was 1,3 cm in this group, 2,8 cm in the midazolam group, and 4,3 cm in the ketamine-alone group.[4]

Intranasally administered ketamine showed an analgesic effect similar to that of opioids at 15 and 60 minutes, although its efficacy was lower at 30 minutes. Compared with placebo, a reduction in pain and a lower need for rescue analgesia were observed.[8] When administered intravenously, ketamine reduced secondary hyperalgesia more effectively than opioids ($p < 0,04$). Furthermore, when combined with morphine, it eliminated the phenomenon of “windup pain” or central sensitization in the affected area ($p < 0,002$).[5]

Table 1. Presentation of results

Type of design	Author	Year of publication	Intervention in the study	Route of administration	Dosage regimen (dose, duration of treatment)	Key results	Conclusion
Systematic review	Billy Sin, et al.[6]	2015	Review of four clinical trials on ketamine in sub-dissociative doses for acute pain in emergencies.	Intravenous (IV)	Subdissociative dose (0,1-0,5 mg/kg), IV bolus followed by continuous infusion in some studies.	Two studies showed less pain and opioid use with ketamine, while others found no difference.	The evidence is limited; further studies are needed to confirm the effectiveness of sub-dissociative doses in emergencies.
Systematic review/meta-analysis	Li X et al.[8]	2021	Monotherapy and combined with opioids	Intranasal (IN)	Dose: 1 mg/kg IN; some studies used fixed doses of 0,5-1 mg/kg or 25 mg	IN ketamine showed opioid-like pain reduction at 15 and 60 minutes, but was less effective at 30 minutes. Compared with placebo, it reduced pain more and decreased the need for additional analgesia.	IN ketamine could be an effective alternative to opioids in the management of acute pain in emergencies, but the evidence remains limited and further studies are needed.
Systematic review/Meta-analysis	Li Wang et al.[1]	2015	Review of 36 clinical trials (2502 patients) evaluating ketamine for postoperative pain in adults.	Intravenous (IV)	Dose ≤1 mg/kg IV or infusion ≤20 µg/kg/min (24-72 hours)	Ketamine reduced pain intensity (0,4-1,3 cm on the VAS scale) and opioid consumption (5-20 mg less in 24-72 hours).	The addition of ketamine slightly improves analgesia and reduces the side effects of opioids, but its clinical impact is limited.
Systematic review/Meta-analysis	Seak et al.[2]	2021	Intranasal ketamine vs. intravenous analgesics (morphine, fentanyl) or placebo	Intranasal (IN)	1 mg/kg intranasal ketamine	Intranasal ketamine showed no significant differences in pain reduction compared to IV analgesics or placebo at different time points (5-60 min). No increased need for rescue analgesia was observed.	Intranasal ketamine is a non-inferior alternative to IV analgesics for acute pain in emergencies, with a favorable safety profile. Further studies are needed to confirm its clinical role.

Systematic Review	Altirkistani et al.[3]	2023	Ketamine vs. opioids for acute pain	Intravenous (IV)	Dose: 0,2-0,5 mg/kg IV, variable time (15-120 min)	Ketamine was not superior to opioids in reducing pain according to the NRS and VAS scales. In 15 minutes, a comparable but not significant effect was observed.	Ketamine is an effective alternative to opioids for acute pain in emergencies, with similar effects on pain relief and an acceptable safety profile.
Randomized clinical trial	Fatih Zor et al.[4]	2010	Ketamine with tramadol and dexmedetomidine vs. midazolam vs. ketamine alone	Intramuscular (IM)	Ketamine: 2 mg/kg IM	The combination of ketamine + tramadol + dexmedetomidine reduced post-procedure pain (VAS: 1,3 vs. 2,8 and 4,3, p < 0,05), adverse effects (11 vs. 27 and 54, p = 0,003), and improved satisfaction (3,6 vs. 3,1 and 2,9, p = 0,018).	The most effective and safest option for pain during dressing changes in severe burns.
Systematic Review	McGuinness et al.[5]	2011	Intravenous ketamine combined with morphine vs. placebo	Intravenous (IV)	0,3 mg/kg/h, bolus followed by continuous infusion	IV ketamine reduced secondary hyperalgesia more than opioids (p < 0,04). Combined with morphine, it eliminated the “windup pain” phenomenon or central sensitization in the affected area (p < 0,002).	IV ketamine is effective against hyperalgesia in burns, but further clinical trials are needed.
Systematic review	Romanowski K.S.[9]	2020	Multimodal analgesia with ketamine in burns	Intravenous (IV)	Low doses as an adjunct	Low-dose ketamine reduced opioid consumption by 30,50 % in some studies (Level D), but the evidence was insufficient to standardize its use. Pain reduction of up to 1,5 cm on the VAS was observed with multimodal analgesia.	The evidence is limited to guide a standard of care, but multimodal analgesia, including ketamine, could optimize pain management in burns.

Randomized clinical trial	Sado-Filho et al.[7]	2019	Compared the combination of ketamine and midazolam with standard opioids for pain management in burn patients	Intranasal	Ketamine 3 mg/kg + midazolam 0,5 mg/kg intranasal or oral, administered 30 minutes before the procedure	The combination of ketamine and midazolam significantly reduced post-procedure pain ($p < 0,05$), with less need for rescue analgesia. There were no significant differences in adverse effects such as hallucinations or dysphoria compared to opioids.	Ketamine combined with midazolam is an effective and safe option for pain management in burn patients, reducing the need for opioids.

The combined use of ketamine and opioids reduced the total consumption of the latter by 5 to 20 mg over a period of 24 to 72 hours, with a reduction in pain of between 0,4 and 1,3 cm on the VAS scale. A lower incidence of postoperative nausea and vomiting was also reported ($p < 0,05$).[1]

On the other hand, intranasal administration of ketamine showed no significant differences in pain reduction compared to opioids or other intravenous analgesics at different measurement times (5-60 minutes). There were also no variations in the need for rescue analgesia.[2]

Safety and adverse effects

The safety profile of ketamine and the occurrence of adverse effects were evaluated in several studies.

In burn patients, the comparison between ketamine and opioids showed no statistically significant differences in pain reduction ($p > 0,05$). However, opioids were associated with a higher frequency of serious adverse effects, while ketamine presented mild and transient adverse events.[3]

A meta-analysis that included 246 studies led to the formulation of 20 recommendations for the management of burn pain. In several of these studies, the administration of low doses of ketamine contributed to a 30-50 % reduction in opioid consumption (Level D). However, the available evidence was insufficient to establish a standard of treatment based solely on its use.[9]

In terms of safety, the most common side effects of ketamine were mild and transient. These included psychomimetic phenomena such as hallucinations, dysphoria, and perceptual disturbances, which could be managed without discontinuing treatment. Combination with other agents, such as dexmedetomidine, reduced the incidence of these adverse effects.[4]

DISCUSSION

This systematic review examines the role of ketamine in the management of acute pain in burn patients, addressing its benefits and risks, adverse effects, routes of administration, and combination with other analgesics. The studies reviewed suggest that ketamine may play a relevant role in analgesia, contributing to a reduction in pain scores and cumulative morphine consumption of up to 23 %.[1] Its action as a non-competitive antagonist of NMDA receptors allows it to modulate secondary hyperalgesia and prevent “windup pain” (central sensitization), which is particularly useful in the context of burn pain.

However, the methodological heterogeneity of the studies makes it difficult to draw definitive conclusions. Differences in the severity of injuries, dosing regimens, and scales used to measure pain could explain the discrepancies observed in the analgesic efficacy of ketamine. While some clinical trials reported statistically significant reductions in pain scores with low doses of intravenous ketamine, others found no relevant differences compared to opioids such as morphine and fentanyl.[5,6]

Among the different routes of administration, intravenous was the most widely used, with bolus doses of 0,1 to 1 mg/kg and a continuous infusion of 0,05 to 0,5 mg/kg/h, providing rapid and sustained relief. Intranasal administration, with doses of 1 mg/kg, showed variable results depending on the clinical context and patient profile, with no significant differences compared to intravenous opioids in some evaluations.[3,5] The intramuscular route, at a dose of 2 mg/kg,

was mainly used for procedures such as debridement and dressing changes. In contrast, the oral route at 5 mg/kg was combined with other analgesics, resulting in reduced pain scores on VAS and NRS scales.

In terms of safety, the most common adverse effects included nausea, vomiting, hallucinations, and delirium, with an incidence ranging from 10 % to 40 %, depending on the dose and route of administration. Although these effects were transient and self-limiting, their presence can pose a challenge in clinical practice, especially in patients requiring continuous infusions for prolonged periods.[2,6] In addition, sustained use of ketamine has been linked to the development of tolerance and risk of dependence, underscoring the importance of adequate monitoring during its administration.

Compared to opioids, ketamine has certain advantages, such as a lower incidence of respiratory depression and greater hemodynamic stability. However, data on its analgesic efficacy relative to opioids are inconsistent. Some studies have reported a significant reduction in opioid consumption with concomitant ketamine use, while others found no statistically significant differences in overall analgesic effect.[6]

The methodological limitations of the studies analyzed, such as small sample sizes, lack of long-term follow-up, and variability in administration protocols, make it difficult to generalize the findings. Future research with multicenter clinical trials, larger samples, and standardized protocols is needed to evaluate the long-term impact of ketamine in the treatment of burn pain.

In conclusion, ketamine appears to be a promising option in the management of acute pain in burn patients, especially as part of analgesic strategies. However, its clinical implementation requires clear protocols, adequate monitoring, and individualized patient assessment.

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FINANCING

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CONFLICT OF INTEREST

None.

AUTHORSHIP CONTRIBUTION

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