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NARRATIVE REVIEW

Efficacy of opioids and non-opioid analgesics in the treatment of post procedure pain of burned patients: a narrative review

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KEYWORDS
Burns;
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Narcotics;
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Abstract
Introduction: Burns are a common trauma that cause acute severe pain in up to 80% of patients. The objective of this narrative review is to evaluate the efficacy of opioids, non-steroidal anti-inflammatory drugs, paracetamol, gabapentinoids, ketamine, and lidocaine in the treatment of acute pain in burn victims.
Methodology: The databases explored were PubMed, Embase, ClinicalTrials, and OpenGrey. The included randomized, controlled clinical trials assessed the analgesic efficacy of these drugs on hospitalized patients, had no age limit, patients were in the acute phase of the burn injury and were compared to placebo or other analgesic drugs. Studies describing deep sedation, chronic opioid use, chronic pain, and patients taken to reconstructive surgeries were excluded. The Jadad scale was used to evaluate quality.
Results: Six randomized controlled clinical trials (397 patients) that evaluated the analgesic efficacy of fentanyl (n = 2), nalbuphine (n = 1), ketamine (n = 1), gabapentin (n = 1), and lidocaine (n = 1) to treat post-procedural pain were included. Fentanyl, nalbuphine, and ketamine were effective, while lidocaine was associated with a slight increase in reported pain and gabapentin showed no significant differences. Two studies were of high quality, one was of medium high quality, and three were of low quality. No studies on the efficacy of NSAIDs or paracetamol were found.
Conclusion: Evidence of efficacy is very limited. Fentanyl, nalbuphine, and ketamine seem to be effective for controlling acute pain in burn patients, whereas gabapentin and lidocaine did not show any efficacy.

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Introduction

Burns are a common type of injury that is associated with morbidity and mortality. In the United States, estimates are that 450,000 people suffer from burn injuries every year. Although most of these injuries are mild, approximately 40,000 people require hospitalization to complete treatment.[1] In Europe, the annual incidence of severe burns is 0.2 to 2.9/10,000[2] and global mortality varies between <1% and 60.8%.[3]

People with second- to third-degree burns experience acute pain due to the injury and the therapeutic procedures carried out to treat the initial burn and other related complications. Along with initial pain, there may be incidental pain with significant severity variation, leading to changes in analgesic requirements.[4] In the acute phase, it is estimated that 84% of patients experience severe to intolerable pain, 100% report daily pain, and 92% suffer night pain that awakens them.[5]

Opioids are generally recommended as the first-line treatment for moderate to severe acute pain in these patients, despite insufficient evidence of their use.[6] There are also co-adjuvant drugs that act on the receptors of the nociceptive pathways and have an additive or synergic action,[7] such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), ketamine, lidocaine, and gabapentinoids.[8]

The management of acute pain in burn patients is a challenge as reports of high-quality analgesia studies are scarce and existing treatment schemes have information gaps.[6] The objective of this narrative review is to evaluate the efficacy of opioids, NSAIDs, paracetamol, gabapentinoids, ketamine, and lidocaine in the treatment of acute pain associated with wound care procedures in burn patients.

Methods

Databases and eligibility criteria

A structured search was done between November 12 and 17, 2019, in PubMed (Medline) and Embase. Unpublished articles were collected from ClinicalTrials and OpenGray. Randomized clinical trials (RCT) of burn patients with clinical treatment indications and/or second-degree burns or higher that met the following criteria were included: evaluation of the efficacy of opioids, non-steroidal anti-inflammatory drugs (NSAIDs) (ketorolac, diclofenac, parecoxib), paracetamol, gabapentinoids, ketamine, lidocaine vs. intravenous, or oral placebo or another drug with analgesic properties used for acute pain relief according to the authors' opinion; a minimum follow-up period of six hours and a maximum follow-up period of 15 days; written in Spanish or English; and assessment of analgesia as a primary or secondary outcome. No filter for age or publication date was applied.

Ketamine trials involving doses of <1 $mg.kg^{-1}$ intravenously or <8 $mg.kg^{-1}$ rectally, as well as and dexmedetomidine <1 $\mu g.kg^{-1}.h^{-1}$ intravenously were considered for inclusion. Studies with intubated patients, anesthetic doses of ketamine at a dose of $\geq$ 1 $mg.kg^{-1}$ intravenously or $\geq$8 $mg.kg^{-1}$ rectally, dexmedetomidine at a dose of $\geq$1 $\mu g.kg^{-1}$, and propofol at a dose of $\geq$1 $mg.kg^{-1}$, or in combination with hypnotic sedative agents used for analgesia or procedural sedation related with the care of burn injuries, studies in patients with chronic use of opioids or previous chronic pain, and studies with burn patients taken to reconstructive surgery were excluded.

Outcomes

Reported pain sensitivity using the verbal numeric scale, the visual analog scale, or the verbal assessment scale was the primary outcome (absent, mild, moderate, severe, intolerable). Based on Woo study, equivalence between these scales was established (1–4 equals mild pain, 5–6 equals moderate pain, and 7–10 equals severe/intolerable pain).[9] The need for rescue analgesia to treat the pain crisis and the side effects associated with the drug used were the secondary outcomes. The full text of the articles included in this study was reviewed to analyze outcomes other than pain control.

Search strategy

The MeSH terms used to conduct the search in Medline-PubMed were ''burns'' AND ''acute pain'' OR ''pain management.'' The subheadings used for the term ''burns'' were ''drug therapy'' OR ''metabolism'' OR ''physiology'' OR ''physiopathology'' OR ''prevention and control'' OR ''therapy.'' In turn, the subheadings used for the term ''acute pain'' were ''drug therapy'' OR ''metabolism'' OR ''physiology'' OR ''physiopathology'' OR ''rehabilitation'' OR ''therapy.'' Finally, for the term ''Pain Management'', the subheadings used were ''adverse effects'' OR ''classification'' OR ''pharmacology'' OR ''therapeutic use'' OR ''therapy.''

Simultaneously, an independent search was conducted with all the drugs of interest for the study using the MeSH term ''burns'' and the Boolean operator AND plus the following MeSH terms: ñarcotics,¨ketamine," "lidocaine," "anti-inflammatory agents, non-steroidal," "acetaminophen," "gabapentin," "pregabalin." The following subheadings were used for each of the drugs: ädministration and dosageÖR ädverse effectsÖR ägonistsÖR änalogs and derivativesÖR äntagonists and inhibitorsÖR c̈lassificationÖR m̈etabolismÖR p̈harmacokineticsÖR p̈harmacologyÖR p̈hysiologyÖR ẗherapeutic useÖR ẗherapy.. Lastly, the following filters were applied to the search: Clinical Trial; Controlled Clinical Trial; Observational Study; Randomized Controlled Trial; studies in humans.

The search in www.clinicaltrials.gov was done using the terms ''burned'', ''burns'' AND ''pain,'' applying the following filters: completed, terminated studies, interventional studies, observational studies. On the other hand, the search in OpenGray was done using the terms ''burn'' and ''burns'', as well as the following filters: medicine (discipline) and Spanish and English languages (Appendix 1).

Study selection process

Two independent reviewers selected the studies based on the titles and abstracts according to the inclusion criteria. These references were included in a result extraction

matrix (Appendixes 2 and 3) and pre-selected studies were thoroughly reviewed. In case of disagreement during the process, a third reviewer decided whether the analysis should be included in the qualitative syntaxis or not. To summarize this information, one of the authors extracted detailed information from each selected study (author, year of publication, name and design of the study, population characteristics, size of the population, pharmacologic intervention, control group, and results evaluated).

Data analysis and synthesis

A narrative approach was utilized to synthesize the findings of the included studies. Data could not be pooled using meta-analytic methods due to their heterogeneity and were thus described individually. The estimation of effect sizes was hampered by a limited data reporting and a high degree of clinical heterogeneity.

Evaluation of biases and heterogeneity

The 5-point Jadad scale[10] was used to assess quality and probability of bias, having in mind randomization, blinding, and description of the reasons for abandonment or exclusion of participants. Since clinical heterogeneity was so strong between studies, no statistical heterogeneity analysis was performed (regarding the drugs used).

Results

Search results

Initially, 540 references were found using the search criteria above mentioned. A total of 127 references were duplicates, consequently, they were excluded. The titles and abstracts of the remaining 413 references were reviewed and 51 were pre-selected. After conducting a thorough full-text review of these articles, six were included in the final analysis (Fig. 1). The methodological quality of the included studies was variable (Table 1).

Description of the studies

High levels of clinical heterogeneity between the studies in terms of the type of drugs used were identified, so a statistical heterogeneity analysis was not performed. Regarding quality, it was found that 2 of the studies scored 5 points, 1 study scored 4, and 3 studies scored below 3.

The six selected studies included 397 patients, of whom 231 received at least one treatment and 166 were assigned to the control group (68 placebo, and 98 another drug). One of the studies evaluated the use of intravenous lidocaine as an adjuvant in postoperative pain management,[11] and another evaluated the efficacy of gabapentin as an adjuvant immediately after thermal injury.[12] One research the efficacy of ketamine for pain management during and after dressing change and compared it to dexmedetomidine while dressings were being changed.[13] Two studies compared the analgesic efficacy of fentanyl changing dressings; one of them reported different doses of the drug through a patient-controlled analgesia pump (PCA),[14] and the other used a pediatric formulation intranasally versus oral morphine.[15] Finally, one study compared the analgesic efficacy of nalbuphine to morphine for pain control during wound care of burn injuries.[16]

Primary outcome

The included studies evaluated analgesic efficacy of gabapentin (n = 1), lidocaine (n = 1), fentanyl (n = 2), nalbuphine (n = 1), and ketamine (n = 1) (Table 2). All of them were carried out to assess analgesic efficacy for pain management during burn care procedures, specifically dressing changes (Table 2).

Kundra[13] randomly assigned patients to 2 groups to receive ketamine 5 $mg.kg^{-1}$ and dexmedetomidine 4 $\mu g.kg^{-1}$ orally (Table 2). When compared to the baseline value, pain intensity decreased by 67% in the ketamine group and 44% in the dexmedetomidine group. Pain scores in the ketamine group were significantly lower than in the dexmedetomidine group ($p < 0.05$) (Table 2).

In Prakash's study,[11] each adult patient (n = 60) received an initial loading dose of fentanyl 1 $\mu g.kg^{-1}$ for 10 minutes intravenously before changing the dressings. During the procedure, patients were given various bolus doses of fentanyl via a PCA pump, finding that the optimal dose was 30 μg per bolus when using a PCA pump, with a total mean fentanyl dose administered of 155.00 ± 40.71 μg. In turn, Borland,[15] in a study with a cohort of 24 pediatric patients, found that intranasal fentanyl (1.4 $\mu g.kg^{-1}$ every 15 minutes) prior to wound dressings was as effective as oral morphine and did not cause respiratory depression. The study concluded that intranasal fentanyl is as effective as oral morphine for pain management during dressing change in pediatric patients.

Furthermore, in a randomized study, Lee et al.[16] compared nalbuphine 0.4 $mg.kg^{-1}$ and morphine 0.2 $mg.kg^{-1}$ intravenously (n = 50), finding no significant differences in the doses used or in pain scores after a wound treatment procedure in burn patients. Wibbenmeyer et al.,[12] on the other hand, compared gabapentin to placebo to identify differences in pain and opioid use (n = 50); the gabapentin group received a daily dose ranging between 300 mg and 3,600 mg. There was no difference in pain scores or opioid use between groups.

Lastly, Wasiak et al.[11] conducted a randomized trial in which they compared the administration of lidocaine 1.5 $mg.kg^{-1}$ intravenously followed by an infusion run at 2 $mg.min^{-1}$ during the dressing process to placebo (n = 45). The difference in pain intensity score was slightly lower for lidocaine [difference (95%CI) = 0.36 (0.17–0.55)] than for placebo.

Secondary outcomes

The six studies evaluated the presence of adverse events associated with drug administration, even though the sample size was not based on this parameter in any of the studies. Rescue analgesia was assessed as an outcome in four of the studies and was defined need for rescue analgesia to manage a pain crisis.

Table 1 Study quality score on Jadad scale.

Author, year	Study name	Quality of the study according to Jadad scale					
		Is the study described as having randomized assigning?	Is the study described as being double blind?	Are the dropouts and exclusions described?	Is the method of randomized assignment the appropriate one?	Is the blinding method the adequate one?	Total score
Wibbenmeyer et al, 2014	Gabapentin is ineffective as an analgesic adjunct in the immediate postburn period	1	1	1	1	1	5
Jason Wasiak et al, 2011	Adjuvant use of intravenous lidocaine for procedural burn pain relief: a randomized double-blind, placebo-controlled, cross-over trial	1	1	1	1	1	5
Prakash et al, 2004	Patient-Controlled Analgesia with Fentanyl for Burn Dressing Changes	1	1	0	-1	1	2
Lee, Marvin, Heimbach, 1989	Effectiveness of nalbuphine for relief of burn debridement pain	1	1	0	-1	-1	0
Kundra et al, 2013	Oral ketamine and dexmedetomidine in adults' burn wound dressing—A randomized double-blind cross over study	1	1	0	-1	-1	0
M.L. Borland et al., 2005	Intranasal fentanyl is an equivalent analgesic to oral morphine in pediatric burns patients for dressing changes: A randomized double-blind crossover study	1	1	1	0	1	4

Table 2 Description of the included studies.

Author, year, tittle, study design	Population	Pharmacologic intervention	Treatment	Comparison	Primary outcome	
					Post procedure pain report	Analgesic efficacy
Wibbenmeyer et al., 2014	Patients older than 18 (n = 53) with a burn injury compromising at least 5% body surface area and a predicted hospitalization of 48 hours.	Gabapentin	Day 1: 1200 mg (only dose).	Placebo	Pain intensity according to Numeric Rating Scale: Average (SD)	There is no difference in the pain intensity reported after procedure between groups
Gabapentin is ineffective as an analgesic adjunct in the immediate postburn period, RCT			Day 2,3: 300 mg TID, 900 mg.day^{-1}		Group I (n = 27) 5.4 ± 2.5	
			Day 4-7 of study: 600 mg TID 1800 mg* Daily. Day 8-11 of study: 800 mg TID 2400 mg* Daily. [Optional raising to 2400 if pain score continues at 4 in NPR scale] Day 11 of study: 1200 mg TID 3600 mg* Daily [Optional raising to 3600 if pain score continues at > 4 in NPR scale]		Group C (n = 26) 5.5 ± 2.5 p = 0,57	
Jason Wasiak et al., 2011	Adult patients (n = 90) admitted to the Victorian Adult Burn Service, with a burn injury affecting between 3 and 55% body surface area. And that were taken to injury care procedures as in: Debridement ± change of dressings in within two days and analgesia was prescribed with opioids as part of the treatment	Lidocaine	Initial Dose: 1.5 mg.kg^{-1} (30 minutes post procedure)	Saline solution 0.9%	Pain intensity according to according to numeric scale (Numeric Rating Scale): Median (RIC)	Mild increment in reported pain in lidocaine group

Table 2 (*Continued*)

Author, year, tittle, study design	Population	Pharmacologic intervention	Treatment	Comparison	Primary outcome	
					Post procedure pain report	Analgesic efficacy
Adjuvant use of intravenous lidocaine for procedural burn pain relief: a randomized double-blind, placebo-controlled, cross-over trial, RCT			Bolus: 0,5 mg.kg^{-1} (two boluses after initial dose every 5 minutes)	Administered in equal volume, dose, and speed as lidocaine		
			Infusion: 2 mg.min^{-1} (during the duration of the changing of dressings)		Group I (n = 45) Group C (n = 45) 1 (0-2) 1 (0-3) Change in NRS	
Prakash et al., 2004	Adult patients (n = 60) with thermal burns of more than 20% body surface area and programmed to the change of dressings	Fentanyl	Initial dose: 1 μg.kg^{-1} (10 minutes before the procedure of every patient) Dose on demand of fentanyl divided in four groups: 10, 20, 30 and 40 μg	PCA-fentanyl demand doses 10, 20, 30, and 40 μg.	Size of demanded dose of fentanyl (μg)	Optimal on demand dose of fentanyl controlled by the patient (PCA) was 30 μg (5-minute interval) after the initial dose of fentanyl 1 IV μg.kg^{-1}
Patient-Controlled Analgesia with Fentanyl for Burn Dressing Changes, RCT					Score VAS scale: average (SD) Group 10 μg: 7.73 (1.33) Group 20 μg: 7.20 (1.21) Group 30 μg: 4.47 (0.83)* Group 40 μg: 3.90 (0.63)* *$P \leq 0,05$	
Lee JJ, et al., 1989	Adult male patients (n = 50) between 18-65 years hospitalized with second and third degree burns and taken to debridement of injuries	Nalbuphine	0,4 mg.kg^{-1}	Morphine 0,2 mg.kg^{-1}	Pain intensity nominal scale: none, mild, moderate, severe	Nalbuphine and morphine have a comparable analgesic efficacy

(*Continued*)

Author, year, tittle, study design	Population	Pharmacologic intervention	Treatment	Comparison	Primary outcome	
					Post procedure pain report	Analgesic efficacy
Effectiveness of nalbuphine for relief of burn debridement pain, RCT					Nalbuphine (n = 25) Morphine (n = 25) p 10 minutes after treatment 2,6 ± 0,2 2,4 ± 0,1 > 0,05 Pain intensity VAS scale: 0 = none, 10 = severe Nalbuphine (n = 25) Morphine (n = 25) p 10 minutes after treatment 4,5 ± 0,6 3,4 ± 0,5. > 0,05	
Kundra et al., 2013	Adult hospitalized patients (n = 120) with a burn injury compromising 20% to 50% body Surface area.	Ketamine (Group K)	5 $mg.kg^{-1}$	Dexmedetomidine 4 $mcg.kg^{-1}$ (Grupo D)	Pain intensity evaluated with visual analog scale: average (SD) Grupo K (n = 60): 2,6 ± 0,6 cm	VAS score was improved in 67% in group K and 44% in group D from baseline values. VAS scores improved significantly in group K vs group D in every time interval, $P < 0.05$
Oral ketamine and dexmedetomidine in adults' burn wound dressing—A randomized double-blind cross over study, RCT					Grupo D (n = 60): 3,8 ± 0,8 cm	
M.L. Borland et al., 2005	Children with burn injury aged up to 15 years (n = 24).	Intranasal fentanyl	1,4 $\mu g.Kg^{-1}$	Oral morphine 1 $mg.kg^{-1}$	Intranasal fentanyl	Intranasal fentanyl is an adequate analgesic agent used in changes of dressings for pediatric burns, by itself or in combination with oral morphine as a titratable agent.

(*Continued*)

Author, year, tittle, study design	Population	Pharmacologic intervention	Treatment	Comparison	Primary outcome	
					Post procedure pain report	Analgesic efficacy
Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomized double blind crossover study, RCT				Group A	Baseline 0 (0–1)	
				(Day 1: oral morphine + intranasal placebo	1 (0–1.3)	
				Day 2: oral placebo + intranasal fentanyl)	0.31	
				Group B	Pre-procedure	
				(Day 1: Intranasal fentanyl + oral placebo	4.3 (0–6)	
				Day 2: oral morphine + intranasal placebo)	2 (1–3.1)	
					0.47	
					Post procedure	
					0 (0–4) a	
					1.5 (0.8–2.5)	
					0.45	
					Data are presented as median and interquartile range a = lost values for a patient b = lost values for two patients	

* Statistically significant difference.

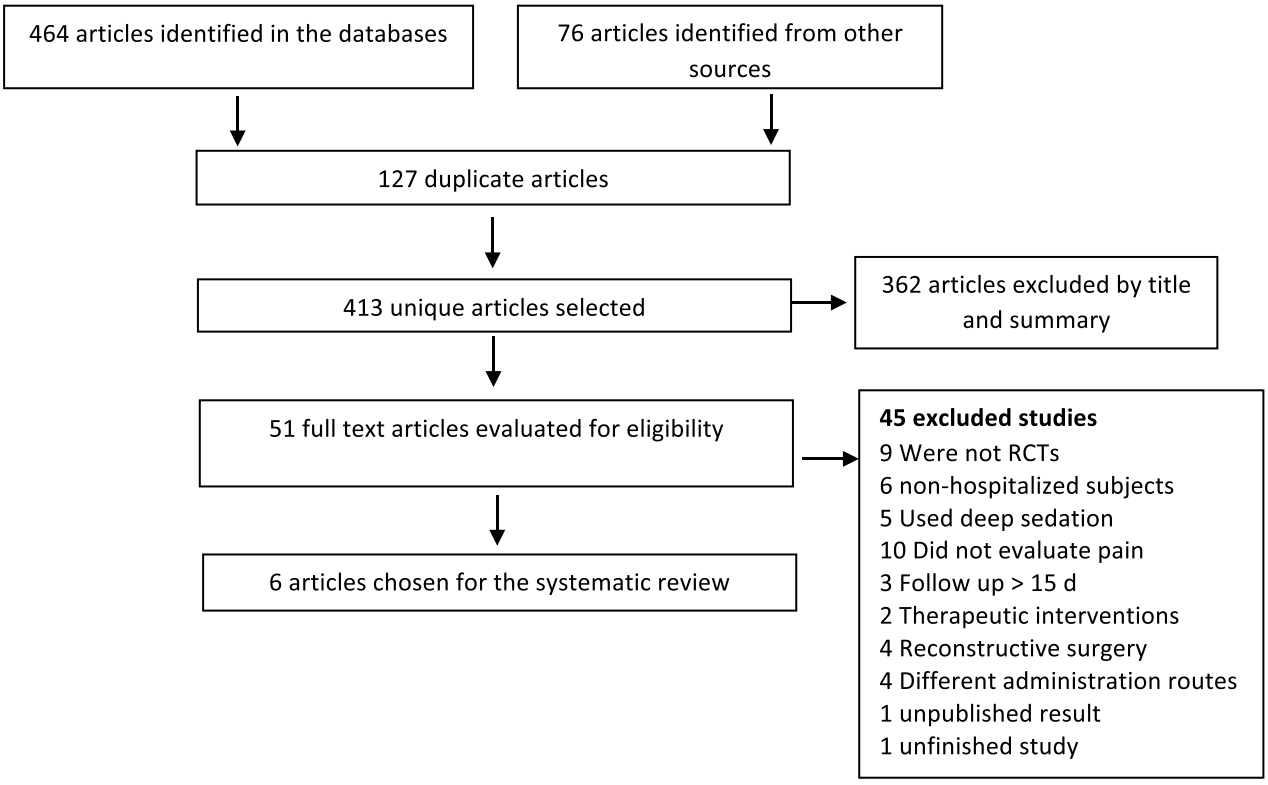

Figure 1 Flowchart diagram.

Firstly, Wibbenmeyer[12] evaluated secondarily the impact of gabapentin on patient anxiety measured using the Hospital Anxiety and Depression Scale (n = 53); no difference in anxiety scores was observed between the placebo group and the gabapentin group (HADS-anxiety $p = 0.13$).

Wasiak et al. (2011),[11] who compared the effect of intravenous lidocaine to placebo, also assessed patient satisfaction (n = 45) with treatment and anxiety in relation to lifestyle changes; no differences in these two aspects were observed in the treatment groups.

Moreover, Lee et al.,[16] in a study with male patients (n = 50) who received morphine or nalbuphine, investigated analgesic acceptability using a categorical scale, finding no differences between analgesic acceptability scores in both groups; this study did not include functional scales.

Kundra et al.[13] carried out a crossover study to compare the effects of oral ketamine to dexmedetomidine (n = 60). The incidence of delirium and excessive salivation was evaluated, finding that they were significantly higher in the ketamine group ($p < 0.05$); however, the post-procedure assessment showed that most patients (63.3%) preferred ketamine over dexmedetomidine ($p < 0.05$). In turn, Prakash et al.[14] reported outcomes other than pain intensity (n = 60), demonstrating that patients who received a dose of 30 μg were satisfied with pain relief.

Finally, Borland et al.[15] performed a crossover study in pediatric patients (n = 24) that compared oral morphine and nasal fentanyl, reporting no statistically significant associations between treatment and certain recovery variables. For example, the average time to resume daily activities were 145 minutes for patients receiving oral morphine compared to an average time of 125 minutes for patients receiving nasal fentanyl.

Discussion

The objective of this narrative review was to evaluate the analgesic efficacy of six drugs or drug groups during wound care in burn patients, namely, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, gabapentinoids, ketamine, and lidocaine. One of the first conclusions drawn from the results is that the clinical trials comparing the efficacy of various pharmacologic treatments for acute pain in burn patients are scarce. However, six studies that met the inclusion criteria evaluated the analgesic efficacy of fentanyl, nalbuphine, gabapentin, ketamine, and lidocaine. Efficacy was assessed in patients whose dressings were replaced during follow-up.

Regarding fentanyl, analgesic efficacy was observed when administrated intravenously via PCA pump[14] or intranasally.[15] Due to the fast onset of its action, fentanyl is often used in burn patients to relieve background and breakthrough pain associated with procedures.[17] Nevertheless, regular administration of opioids has been linked tolerance, dependence, and abstinence after suspension, so they must be used as part of a multimodal scheme that allows reducing the doses.[18]

In this regard, the ketamine–propofol combination is the most commonly used drug combination for procedural sedation and analgesia in the treatment of burns in children.[19] Since nasal fentanyl spray is not available in many countries, its use may be limited; however, fentanyl citrate for intra-

venous use, due to its lipophilic nature, can be successfully administered by nasal route.[20] While this result indicates a mechanism for scheduling an appropriate dose within the analgesic plan for burn victims, it should be interpreted with caution due to the poor methodological quality of the Jadad score. Despite being prescribed for the treatment of acute continuous pain,[21] no studies comparing the efficacy of opioid drugs to other agents, such as methadone or tapentadol, were identified.

The lack of information on patients receiving hospital-based care and prolonged exposure to opioid use clearly indicates the need for further studies on this issue in burn patients. Few studies evaluate the role of agonists-antagonists. Only a randomized clinical trial compared the efficacy of nalbuphine vs. morphine[16] and was published in 1989; delving into this topic would open the door to new findings in this area.

Kundra et al. conducted a report on ketamine.[13] These researchers found that, compared to dexmedetomidine, ketamine is more effective for pain control, reducing pain intensity in approximately 3 out of every 4 patients. A systematic review published in 2011 that included 4 experimental studies involving voluntary subjects had already established the analgesic efficacy of ketamine in burned patients, demonstrating a decrease in secondary hyperalgesia and pain amplification.[22] The randomized clinical trial included in the present review had a low-quality evaluation score; however, it has an additional value because it includes hospitalized patients, implying that the findings can be applied to clinical practice.

It should be noted that adverse effects were more frequent (mild delirium and excessive salivation) and statistically significant in the ketamine group, without indicating whether these secondary effects forced its suspension. Ketamine has been linked to psychiatric side effects such as hallucinations, delirium, increased secretions, and sympathetic activation, resulting in tachycardia and higher blood pressure, especially at doses higher than 1 $mg.kg^{-1}$.[18]

Regarding lidocaine, although it has been demonstrated that it has analgesic, anti-hyperalgesia, anti-inflammatory, and opioid-sparing effects,[4,23] only one study, published by Wasiak et al.,[11] evaluated its effect as an analgesic adjuvant for burn patients in the acute phase. This trial showed that when lidocaine was added to PCA, the pain level increased compared to the placebo. While clinically irrelevant, the fact that the average improvement in pain score was less than 1 on the visual analog scale makes evident the importance of being cautious when selecting patients for treatment with this drug.

Furthermore, Wibbenmeyer et al.[12] found no significant difference in pain severity following wound treatment when comparing gabapentin to placebo. This finding is consistent with the findings of a historic cohort reported in 2019 that suggested that the early (less than 72 hours after burn injury) or later use of gabapentin does not improve the short- or long-term hospital discharge of burned patients[24]; this result agrees with several investigations on gabapentinoids that show little benefit and the presence of side effects. Consequently, the use of opioids to treat acute pain in burn patients should be reconsidered since up to 60% of the patients experience adverse effects (particularly drowsiness and fatigue).[25] There was no study assessing the impact of pregabalin that could be included in the current analysis.

This review has various strengths. To the best of the authors' knowledge, this is the first study of its kind that evaluates the efficacy of a group of drugs used to treat acute postoperative pain in burned patients and is based on strict inclusion criteria that allowed selecting studies that could be applied to clinical practice. The included studies were randomized controlled clinical trials of hospitalized patients, excluding patients with experimental burns induced under laboratory conditions, and assessed drugs commonly used for acute pain management. Moreover, there were no restrictions on the publication dates of the studies, and unpublished articles were actively searched for in two databases, minimizing the probability of publication bias.

On the other hand, one of the reported weaknesses of the present review is that statistical heterogeneity was not calculated due to the clinical heterogeneity of the findings; as a result, no meta-analysis was performed using the collected data. Another shortcoming was the use of the publication language filter, which limited the number of controlled clinical trials retrieved to English and Spanish only.

Most of the articles included in this review do not address multimodal analgesia, which is widely used today,[4] and involve NSAIDs, dipyrone and acetaminophen as part of the analgesic scheme. In addition, although with limited evidence, intravenous lidocaine infusions may be a useful treatment option in some patients.[26] Intravenous ketamine in sub-anesthetic doses is also recommended in patients who have developed an opioid tolerance.[27] However, due to the high intensity of pain and exposure to multiple painful procedures, non-pharmacological therapies that contribute to analgesia should be considered, such as virtual reality. In this regard, Lauwens et al.[28] found that virtual reality had an outstanding effect in reducing pain in pediatric patients when compared to traditional care (n = 104) ($p < 0.00001$).

Solid recommendations for analgesia in burn patients cannot be made based on the studies included in this review since they involved a small number of patients, efficacy was described as a decrease in the use of opioid analgesics in some studies and a decrease in pain in others, and patient characteristics were quite different. Additionally, non-opioid analgesics are often difficult to compare because of the variety of drugs and doses used in clinical trials. Based on these considerations, the authors propose using fentanyl for background and breakthrough pain and ketamine in subanesthetic doses for breakthrough pain. In a multimodal approach, acetaminophen and nonsteroidal anti-inflammatory medications are viable options.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjane.2021.07.022.

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