BURNS 49 (2023) 1534–1540

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/burns

The risks of sedation and pain control during burn resuscitation: Increased opioids lead to over-resuscitation and hypotension

John M. McClellan [a,1,*], Eloise Stanton [b,1], Jessie O'Neal [a], Jeffrey Anderson [c], Clifford Sheckter [d,e,1], Samuel P. Mandell [f,1]

[a] UW Medicine Regional Burn Center, Harborview Medical Center, University of Washington, USA
[b] Division of Plastic & Reconstructive Surgery, University of Southern California, USA
[c] Department of Surgery, Temple University, USA
[d] Department of Surgery, Stanford University, USA
[e] Regional Burn Center, Santa Clara Valley Medical Center, USA
[f] Parkland Burn Center, University of Texas Southwestern, USA

ARTICLE INFO

Article history:
Accepted 9 August 2023

Keywords:
Burn
Resuscitation
Sedation

ABSTRACT

Introduction: Pain management and sedation are necessary in severely burned persons. Balancing pain control, obtundation, and hemodynamic suppression can be challenging. We hypothesized that increased sedation during burn resuscitation is associated with increased intravenous fluid administration and hemodynamic instability.

Methods: A retrospective review of a single burn center was performed from 2014 to 2019 for all admissions to the burn unit with > 20% total body surface area (TBSA) burns. Within 48 h of admission, we compared total amounts of sedation/pain medications (morphine milligram equivalents (MME), propofol, dexmedetomidine, benzodiazepines) with total resuscitation volumes and frequency of hypotensive episodes. Resuscitation volumes and frequency of hypotension were modeled with multivariable linear regression adjusting for burn severity and weight.

Results: 208 patients were included with median age of 43 years (IQR 29–55) and median %TBSA of 31 (IQR 25–44). Median 48-hour resuscitation milliliters per weight per %TBSA were 3.3 (IQR 2.28–4.92). Pain/sedative medications included a combination of opioids in 99%, benzodiazepines in 73%, propofol in 31%, and dexmedetomidine in 11% of patients. MMEs were associated with greater resuscitation volumes (95% CI: 0.15–0.54, $p = 0.01$) as well as number of hypotensive events (95% CI: 1.57–2.7, $p < 0.001$). No associations were noted with other sedative medications when comparing the number of hypotensive events and resuscitation volumes.

* Correspondence to: Assistant Professor of Surgery, USUHS, Bethesda MD, Clinical Assistant Professor of Surgery, UW, Seattle, WA, USA.
E-mail address: john.mcclellan3@gmail.com (J.M. McClellan).
[1] Authors contributed equally to manuscript

https://doi.org/10.1016/j.burns.2023.08.005
0305-4179/Published by Elsevier Ltd.

Conclusions: Increased opioid administration has physiological consequences and should be carefully monitored during resuscitation as higher volume administrations lead to worse outcomes. Opioids and sedating medications should be titrated to the least amount needed to achieve reasonable comfort and sedation.

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1. Introduction

Pain management and sedation are necessary in severely burned persons to provide comfort and mitigate the effects of pain on recovery and healing [1]. Burn patients often require endotracheal intubation [2], which necessitates sedation for ventilator synchrony [3]. After admission, multiple procedures are performed including bronchoscopy [4], escharotomy [5], wound debridement, and surgical treatments [6]. All these interventions cause considerable pain and discomfort [7] that warrant medical management. Appropriate pain control is associated with improved wound healing, quality of life, sleep, and recovery in burn patients [8,9].

Pain and sedating medications also cause hemodynamic instability through decreasing systemic vascular resistance, inducing vasoplegia, and decreasing cardiac output [6,10]. Burn resuscitation is characterized by hypovolemic shock which may be compounded by the addition of distributary shock from the addition of pain medication and sedatives [11,12]. Excess fluid resuscitation in response to the compounded shock can subsequently lead to worsening edema and resultant complications [13] including acute respiratory distress syndrome (ARDS), abdominal compartment syndrome, extremity compartment syndrome, multisystem-organ failure, sepsis, pneumonia, and death [14].

Balancing pain management, obtundation, and hemodynamic support can be challenging. While pain causes agony for patients and can hinder healing and recovery, overly aggressive management carries substantial hemodynamic risk leading to over-resuscitation. We aimed to investigate the relationship between pain/sedation medication dosing and resuscitation volumes. We hypothesized that increased sedation during burn resuscitation would be associated with increased hemodynamic instability and increased intravenous fluid administration.

2. Methods

2.1. Dataset

This study was approved by an Institutional Review Board at Harborview Medical Center and University of Washington. The Regional Burn Center at Harborview is the only facility providing burn care to a five-state catchment in the US Pacific Northwest. A retrospective chart review was performed from 2014 to 2019 for all admissions to the ICU with $\geq$ 20% total body surface area (TBSA) isolated burn injuries. All patient ages with or without inhalational injury were included. Patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, frostbite, death within 48 h, and acute intoxication (e.g. alcohol, amphetamines) were excluded. Within 48 h of admission, we compared total amounts of sedation/pain medications administered per patient per kilogram. Total opioid doses, both oral and intravenous, were converted to morphine milligram equivalents (MME) in order to facilitate comparisons across different types of opioids (e.g. hydromorphone, fentanyl, hydrocodone, etc.) [15]. Notably, patients get multimodal pain control in addition to opioids, including acetaminophen and ibuprofen (when not concerned about renal failure or a history of gastric bleeding). Gabapentin is also commonly used as an adjunctive analgesic medication; however, it is usually not administered during the first 48 h post-burn.

Benzodiazepine doses were converted to a common lorazepam dosing to facilitate comparisons across different types of benzodiazepines (e.g. midazolam and lorazepam). Other sedatives included propofol and dexmedetomidine. Total resuscitation volumes are collected after all resuscitations and maintained with the burn system database. Hemodynamic data were extracted from the electronic medical record through prespecified criteria for hypotension requiring intervention which is a mean atrial pressure (MAP) of $<$ 65 mmHg [16]. As is standard practice at our institution, a volume assessment was conducted in hypotensive patients, which consisting of a point-of-care ultrasound and evaluation of pulse pressure variation and shock index. In patients who otherwise appear euvolemic, we start vasopressin, which is our traditional first-line vasopressor for volume-refractory hypotension in early burn resuscitation.

2.2. Variables and analysis

Our primary outcome was total 48-hour volume resuscitation (milliliter/kilogram/TBSA) including all intravenous fluids (crystalloid and colloid). Our secondary outcome was the number of hypotensive events that occurred in the first 48 h of admission. Predictor variables included the total dose of sedating/pain medications given during the resuscitation including opioids, benzodiazepines, propofol, and dexmedetomidine. We assumed that dosing administration of these sedatives was independent, and we assumed that there was no interaction between these medications such a synergistic effect on blood pressure between two sedatives. We evaluated the effects of sedating/pain medications on resuscitative volumes and number of hypotensive episodes using linear regression with each type of sedative acting as a continuous covariate. Inhalation injury was added as an additional covariate given its association with increased resuscitative volumes. Intoxicated patients were excluded given the known effects of alcohol and amphetamines on resuscitative volumes. Analysis was performed using Stata 15 (StataCorp LLC, College Station, TX).

Table 1 – Patient, Injury, and Resuscitation Characteristics.

	Median (n = 208)	IQR	Range
Age (years)	43	29–55	2–99
Male sex – no. (%)	142 (68%)	-	-
Weight (kg)	82	66–99	13–176
CDC Index	0	0–0	0–8
%TBSA (> 20%)	31	25–44	20–93
48 hr Resuscitation (ml/kg/%TBSA)	3.9	2.3–4.9	0.1–19
Intubated – no. (%)	61 (29%)	-	-
Inhalational Injury – no. (%)	51 (25%)	-	-
Hypotensive Episodes (no.)	2	0–6	0–73
Death – no. (%)	27 (13%)	-	-

25–75 percentile interquartile range
CDC Index=Charlson Deyo Comorbdity Index

3. Results

A total of 208 patients met inclusion criteria. The median age of the study cohort was 43 (IQR 29–55) with 68% males and 32% females (Table 1). The median weight (kg) of the study population was 82 kg (IQR 66–96 kg). The majority of the patients were White (n = 167, 80.3%), followed by Unknown (n = 15, 7.2%), Black or African American (n = 10, 4.8%), then Asian (n = 7, 3.4%), American Indian or Alaska Native (n = 6, 2.9%), Multiple Races (n = 2, 1.0%), and Native Hawaiian or Other Pacific Island (n = 1, 0.5%). The median % TBSA was 31.0 (IQR 25–44). Over a quarter of patients (n = 61, 29%) were intubated upon admission to the burn intensive care unit (ICU). 25% (n = 51) had a smoke inhalation diagnosed on bronchoscopy.

Median 48-hour resuscitation milliliters per weight per %TBSA were 3.9 (IQR 2.3–4.9) (Table 1), and the mean was 3.3 (Fig. 1). Pain/sedative medications included a combination of opioids in 99%, benzodiazepines in 73%, propofol in 31%, and dexmedetomidine in 11% of patients. The mean MME/KG was 1.9, and the median was 1.0, clinically equating to a 100 kg person receiving 100 mg of morphine (Fig. 2). The mean number of hypotensive episodes was 2 (SD: 10.2, range 0–73), with most patients remaining normotensive (Fig. 3).

Looking at the linear fit between resuscitative volumes and MME showed resuscitative fluids increased as a function of MME (Fig. 4). Similarly, looking at the frequency of hypotensive episodes showed increasing events as MME increased. The linear model evaluating the effects of pain/sedative medications on resuscitation showed that MME, propofol, and dexmedetomidine all had positive coefficients, but only MME demonstrated a significant relationship (coef 0.30, 95% CI 0.10–0.51, $p < 0.01$) (Table 2). Benzodiazepines showed a negative coefficient, but this was not statistically significant. Inhalation injury had a positive coefficient, but it was not significant either. For the linear model evaluating the effects of pain/sedative medications on hypotensive episodes, both MME and dexmedetomidine had positive coefficients which were also statistically significant (MME coef 2.39, 95% CI: 1.63–3.15, $p < 0.01$; dexmedetomidine coeff 0.01, 95% CI: 0.01–0.02, $p = 0.04$) (Table 3). Benzodiazepines and propofol had negative coefficients but were not significant.

4. Discussion

The findings of this study highlight the intricate relationship between the management of pain and sedation and hemodynamic instability. Our analysis demonstrated that the quantity of opioids as measured by MME was significantly associated with both increased number of hypotensive events and resuscitation volumes when accounting for burn size and weight of the patient. Interestingly, this association was not found with any other sedatives/pain medications included in the study such as propofol or dexmedetomidine.

The relationship between increased opioid administration and increased fluid requirements has been previously described in the literature as "Opioid Creep." Sullivan et al. (2004) identified a strongly positive correlation between opioids received and fluids administered [17]. This finding was later substantiated by Wibbenmeyer et al. (2010), who similarly found a strong linear relationship between opioid equivalents administered in the first 24 h post-burn injury and the amount of resuscitation fluids given during this same period [18]. The authors of these studies postulate that higher doses of opioids may have hemodynamic consequences, which may in turn contribute to the increased fluid volumes required. Our current study corroborates this phenomenon and provides additional evidence for the relationship between opioids and hypotension/resuscitation volumes even when adjusting for other sedating medications received such as dexmedetomidine.

Pain secondary to thermal injury has been argued as the most difficult to treat of all noxious stimuli [6,19]. While opioids remain the most used modality for pain management in hospitalized burn patients, they can carry significant pharmacokinetic changes during the hypermetabolic and hyperdynamic processes of burn recovery. Studies have demonstrated that opioids and sedatives have increased clearance and volumes of distribution in burn patients [11,20,21], and thus can lead to increased medication requirements and subsequently risk of greater hemodynamic consequences. In addition, higher doses of opioids can lead to hyperalgesia and longer-term pain-relief requirements; this can be somewhat mitigated by multimodal analgesia, such as with a combination of opioids with dexmedetomidine [11,22]. However, the addition of such alpha2-agonists can lead to potentiation of side effects such as decreased systematic vascular resistance. This in turn has been demonstrated to lead to additional complications in burn injury recovery [23,24]. Benzodiazepines, while lacking analgesic properties, have also been established as a valuable adjunct in burn pain management as studies have shown that anxiety is associated with decreased pain tolerance and subsequently leads to increased utilization of pain medication [25,26].

As aforementioned, the results of our study indicate that greater episodes of resuscitation volumes were only identified with increased MME, while neither propofol, benzodiazepines, nor dexmedetomidine conferred this outcome. This not only disputes our hypothesis but also challenges a

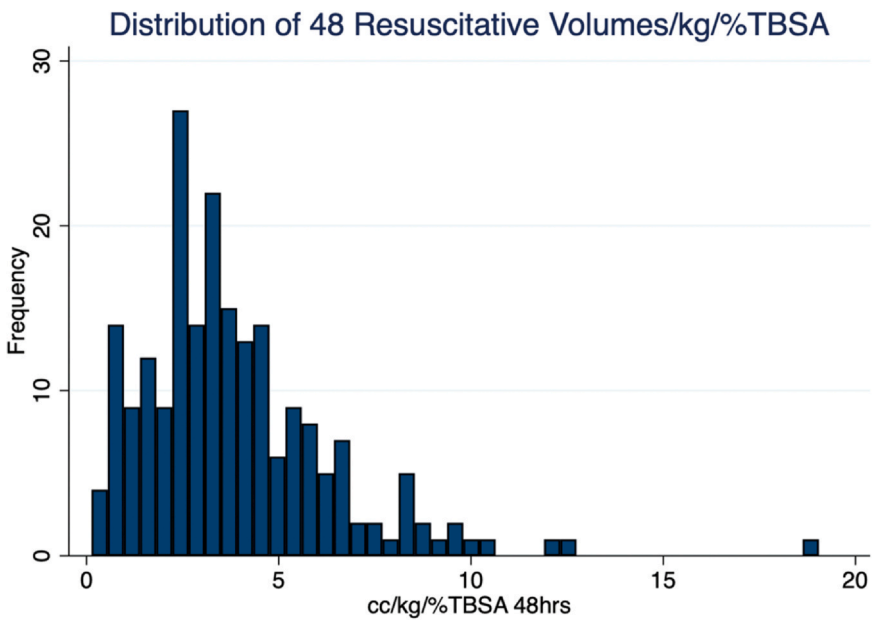

Fig. 1 – Linear Histogram of 48-hr Resuscitation Volumes defined as m/kg/%TBSA.

common clinical practice concern where propofol is often expected to cause hypotension in ICU, which in theory may lead to more fluid administration. However, challenging prior studies [27], we found that dexmedetomidine was an independent risk factor for hypotension in our model despite only 11% of our population receiving this medication. This correlates clinically, as it is not a common medication to use during resuscitation due to its hemodynamic suppression, most notably bradycardia and hypotension [24].

In contrast to the limited existing data on the relationship between propofol, benzodiazepines, and dexmedetomidine and hemodynamic instability, there is a well-described relationship between opioids and hemodynamic effects in critically ill patients [11]. Opioids acutely lead to μ-receptor-mediated vasodilation and subsequent rapid-onset hypotension. Further, opioids have been identified to lead to cardiovascular depression through the release of opioid peptides, including endorphins, enkephalins, and dynorphins, with vasoactive properties that

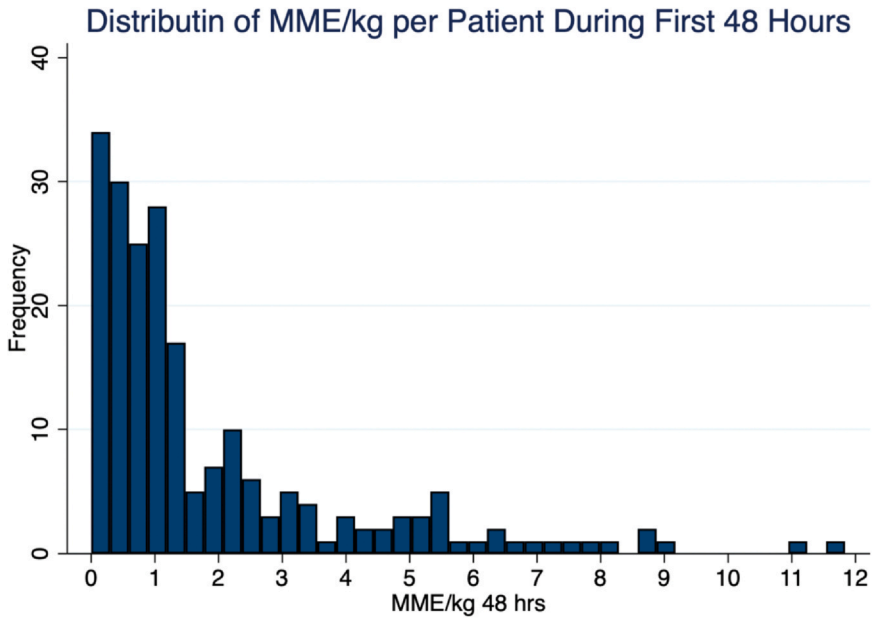

Fig. 2 – Linear histogram of Morphine Milligram Equivalents per Kilogram During the First 48-Hours.

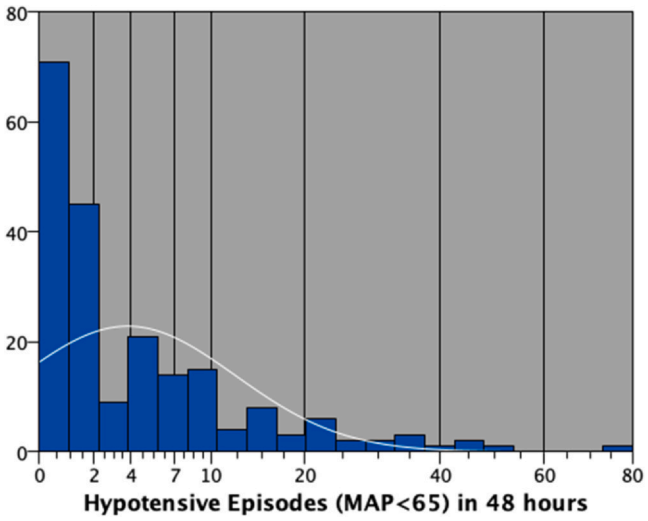

Fig. 3 – Distribution of Hypotensive Episodes (MAP < 65) Among Patients in the First 48-Hours.

Table 2 – Resuscitation Volumes: Multivariable Linear Regression Evaluating Effects of Sedatives and Opioids on Resuscitative Volumes within the First 48 h.

Sedative	Coefficient (95% CI)	p-value
Propofol	0.01 (−0.01 to 0.01)	0.98
MME	0.30 (0.10 – 0.05)	**< 0.01**
Benzodiazepine	-0.01 (−0.02 to 0.01)	0.83
Dexmedetomidine	0.01 (−0.01 to 0.01)	0.31
Inhalation injury	0.56 (−0.26 to 1.39)	0.18

Table 3 – Hypotensive Episodes: Multivariable Linear Regression Evaluating Effects of Sedatives and Opioids on Number of Hypotensive Events within the First 48 h.

Sedative	Coefficient (95% CI)	p-value
Propofol	-0.01 (−0.01 to 0.01)	0.12
MME	2.39 (1.63 – 3.15)	**< 0.01**
Benzodiazepine	-0.05 (−0.11 to 0.01)	0.09
Dexmedetomidine	0.01 (0.01 – 0.02)	**0.04**
Inhalation Injury	0.94 (−2.10 to 3.99)	0.54

are also found in the human heart [28,29]. Accordingly, our data demonstrated that opioids were significantly associated with a greater number of hypotensive episodes. Thus, we advocate for more judicious use of opioids which at higher doses can lead to profound hypotension through cardiovascular suppression. To offset the decreased opioid dosage, in such cases, greater emphasis can be placed on other multimodal analgesics.

There is literature supporting increased resuscitation volumes because of increased opioids [18]. Our results confirm this finding that MME was an independent predictor of increased resuscitation in the first 48 h. It must be noted, however, that there are several factors that also contribute to over-resuscitation in the literature. For example, pre-burn center fluid loading and inadequate communication between the referring physician and the accepting burn surgeon have been identified to lead to surplus fluid administration [14]. An attempt to control for such factors and subsequently minimize confounding variables may help isolate and clarify the role of opioid administration on over-resuscitation and its associated morbidities.

In our intensive care unit, sedation is titrated between − 1 to + 1 using Richmond Agitation-Sedation Scale (RASS) scores [30]. Given the complexity of sedation and pain management

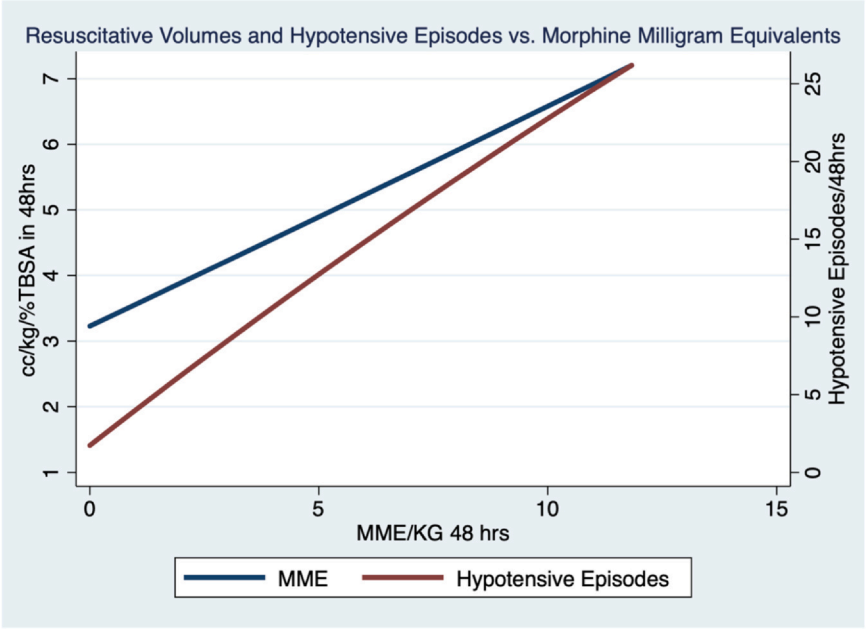

Fig. 4 – Plot of Morphine Milligram Equivalents and its Relationship with Resuscitation and Hypotensive Episodes using a Best Fit Line.

in burn patients, as highlighted by this study, goal RASS scores should remain between 0 to −1, rather than attempting deeper sedation. This would allow for a more accurate assessment of patients' clinical status and beget more careful management. If a patient requires more sedation, next steps should include the use of pressors and cessation of intravenous fluids as long as there is confidence that the hypotension is a result of the opioids and not true hypovolemia. In patients who have a RASS score of 3–4 despite routine doses and drip rates of sedatives and opioids, it is our standard of practice to treat our patients with as-needed haloperidol. However, we do not schedule enteral antipsychotics such as olanzapine or quetiapine. In addition, in the initial 48-hour resuscitation period, our protocol currently does not include administration of ketamine, in part due to the high rates of methamphetamine use in our patient population. Although, we do find it as a useful adjunct later in the hospital course and could be considered as an adjunct during acute burn resuscitation.

These data do not provide a reason for why particular patients received more sedation/pain medications than others. There are plausible reasons including variations in physician orders, nursing practices, or patient-related factors. Patients that require more MME may have more painful burns per weight per TBSA that somehow signals a worse injury. Patients who are intoxicated with amphetamines may be more difficult to sedate, which could possibly be driving higher sedation and resuscitation.

4.1. *Limitations*

This study was retrospective in nature and thus the relationship between certain sedating medications and resuscitation volumes is correlative and causative. As such, a prospective study is necessary to definitively determine whether dexmedetomidine, when used as a sedative, contributes to higher resuscitation volumes. It would be highly unlikely, however, to consider a mechanism whereby increased resuscitation volumes lead to increased opioid administration. A prospective study randomizing burn patients to differing sedation regimens and RASS scores could more definitively answer the extent of causality.

5. Conclusion

Pain management and certain sedative medications (i.e., dexmedetomidine) have physiological consequences and should be carefully monitored during resuscitation as higher volume administrations lead to worse outcomes. Disputing concerns of clinical practice, propofol was not associated with increased resuscitation or hypotension. However, dexmedetomidine was associated with increased hypotension, both challenging previous literature and correlating clinically. Finally, opioids can lead to detrimental hemodynamic consequences.

External funding

No external funding was received in relation to this manuscript.

Declaration of Competing Interest

The authors report no conflicts of interest or financial disclosures related to this manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.burns.2023.08.005.

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