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Risk factors for hypotension in urgently intubated burn patients☆

Christopher J. Dennis [a], Kevin K. Chung [b,*], Seth R. Holland [a], Brian S. Yoon [c], Daun J. Milligan [a], Stephanie L. Nitzschke [b], Christopher V. Maani [b], Jacob J. Hansen [b], James K. Aden [b], Evan M. Renz [b]

[a] Brooke Army Medical Center, Fort Sam Houston, TX, United States
[b] United States Army Institute of Surgical Research, Fort Sam Houston, TX, United States
[c] William Beaumont Army Medical Center, El Paso, TX, United States

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ABSTRACT

Background: When urgently intubating patient in the burn intensive care unit (BICU), various induction agents, including propofol, are utilized that may induce hemodynamic instability.
Methods: A retrospective review was performed of consecutive critically ill burn patients who underwent urgent endotracheal intubation in BICU. Basic burn related demographic data, indication for intubation, and induction agents utilized were recorded. The primary outcomes of interest were clinically significant hypotension requiring immediate fluid resuscitation, initiation or escalation of vasopressors immediately after intubation. Sec ondary outcomes included ventilator days, stay length, and in hospital mortality.
Results: Between January 2003 and August 2010, we identified 279 urgent intubations in 204 patients. Of these, the criteria for presumed sepsis were met in 60% ($n = 168$) of the intubations. After intubation, 117 patients (42%) experienced clinically significant hypoten sion. Propofol (51%) was the most commonly utilized induction agent followed by etomidate (23%), ketamine (15%), and midazolam (11%). On multiple logistic regression, %TBSA (OR 1.016, 95% CI 1.004 1.027, $p < 0.001$) and presumed sepsis (OR 1.852, 95% CI 1.100 3.117, $p = 0.02$) were the only significant predictors of hypotension. None of the induction agents, including propofol, were significantly associated with hypotension in patients with or without presumed sepsis.
Conclusions: In critically ill burn patients undergoing urgent endotracheal intubation, spe cific induction agents, including propofol, were not associated with clinically significant hypotension. Presumed sepsis and %TBSA were the most important risk factors.
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1. Introduction

For critically ill patients who develop respiratory distress and undergo emergent intubation in the intensive care unit (ICU), rapid sequence induction of sedation, analgesia, and paralysis are often used. Commonly used pharmacologic agents provide amnesia and blunt sympathetic responses and may facilitate airway manipulation while endotracheal intubation is performed [1]. Frequently used induction agents include benzodiazepines, opioids, etomidate, propofol, ketamine,

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* *Corresponding author at*: US Army Institute of Surgical Research, 3698 Chambers Pass, Fort Sam Houston, TX 78234, United States. Tel.: +1 210 916 3054; fax: +1 210 271 0830.
E mail address: Kevin.chung@us.army.mil (K.K. Chung).

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and various paralytics. Induction agents, either used in combination or as a single agent, each have a different side effect profile which should engender careful consideration of a compilation of various drug and patient related factors prior to their use. For example, the use of propofol for induction has generally been considered relatively contraindicated in patients who have hemodynamic instability or are otherwise considered critically ill. In 2000, Benson et al. investigated the effects of induction agents on blood pressure, heart rate, and arterial oxygen saturation [1]. In this study, 8078 endotracheal intubation procedures were retrospectively evaluated. The investigators reported that out of all the mainstream induction agents, propofol caused the most significant decrease in mean arterial pressure (MAP) in American Society of Anesthesiologist (ASA) physical status classification system II patients. Earliest data in both in vivo and in vitro models suggest that the main reason for the drop in blood pressure (BP) results from arterial vasodilatation and its subsequent decreased systemic vascular resistance (SVR) [2]. There has been a recent suggestion that propofol may also decrease BP via other mechanisms, such as reducing cardiac output (CO) via myocardial depression or reducing preload via increased venous capacitance [3].

Multiple investigators have shown that there is extensive and sustained release of inflammatory mediators in the post burn period [4,5]. This, in combination with the fluid shifts that occur either in the immediate post operative period following burn wound excision under general anesthesia or during episodes of sepsis, creates a milieu that could make these patients particularly vulnerable. It is therefore reasonable to predict that the hemodynamic effects of propofol may be more pronounced in severely burned patients who develop respiratory distress.

In our own burn intensive care unit (BICU), we observed significant hypotension in a number of patients requiring urgent endotracheal intubation for respiratory distress. Thus, we sought to investigate and describe the various risk factors that may predict the development of hypotension after rapid sequence induction and endotracheal intubation in those critically ill burn patients who develop respiratory distress after admission to the BICU.

2. Methods

After local institutional review board approval, a retrospective chart review of the Military Electronic Medical Record (ESSENTRIS) was performed. The parameters of this search included all patients admitted to the BICU from 1 January 2003 to 30 August 2010 who were urgently or emergently intubated while in the BICU. Urgent or emergent intubations were performed in patients who developed respiratory distress while in the BICU. The intubation status was determined by the presence of an anesthesia or primary team procedure note indicating that endotracheal intubation was performed. Children and patients intubated prior to admission to the BICU were excluded from our search parameters.

Upon identification of patients who met our enrollment criteria, we recorded each patient's age, gender, % total body surface area (%TBSA) burned, presence of inhalational injury, burn thickness, date and time of intubation, presence of presumed sepsis, injury type (thermal or electrical burn, toxic epidermal necrolysis, and other), the induction agent used for intubation and determination whether the patients became hypotensive following intubation. For our study, a clinically significant hypotensive episode was defined as hypotension requiring intervention in the form of starting a new vasopressor, increasing the dose of a current vasopressor, or giving a fluid bolus of at least 500 mL crystalloid or 250 mL of colloid at any time within 1 h immediately following intubation. Those initiated on empiric antibiotics, specifically excluding those who received surgical prophylaxis, in the period 24 h before or after intubation were identified as having presumed sepsis. The primary outcome measure was the development of hypotension. Secondary outcome measures were death from any cause, ICU days, and ventilator days. For these data, exploratory data analyses were performed using summary measures including percentages, means, and medians. Univariate data analysis was performed to determine the significance of any findings identified during the exploratory phase. Dichotomous variables were assessed using a chi square or Fisher's exact test as appropriate, whereas continuous variables were assessed using Student's t test (parametric data) or Wilcoxon rank sum test (non parametric data). In additional, a multiple logistic regression analysis was performed to analyze the relationship between independent variables (age, gender, %TBSA, full thickness, inhalation injury, induction medications, and presumed sepsis) and hypotension.

3. Results

A total of 1516 patients were admitted to the BICU from 1 January 2003 to 30 August 2010. We identified a total of 279 intubations in 204 patients who met our criteria for inclusion in our analysis. Of these, 73% were initial intubations, whereas the remainder of patients had repeat intubations. The main patient characteristics are reported in Table 1.

The most commonly used induction agent was propofol, with paralytic agents being the second most commonly used (Fig. 1). Of the 147 intubations for which paralytics were used, rocuronium was the most frequent (n 116), followed by vecuronium (n 26), succinylcholine (n 3),

Table 1 – Demographic data for intubated patients in the burn intensive unit.

Characteristic	Total patients (n 279)
Age (years)	43 (±19.9)
% Total body surface area	37.9 (±23.2)
Gender (% male)	166 (59.5%)
Inhalation injury	72
Induction agent	
Propofol	143
Fentanyl	27
Versed	30
Etomidate	64
Ketamine	41
Paralytics	147

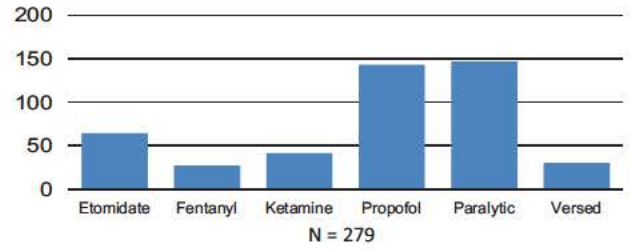

Fig. 1 – Induction agents used for intubation in critically ill burned patients.

and cis atracurium (*n* 2). In those who received propofol as the sole agent for induction (*n* 124), the average MAP decreased from 94 ± 25 mmHg pre intubation to 89 ± 21 mmHg post intubation (*p* 0.037). The average MAP over a 12 h period peri intubation is plotted in Fig. 2, and a significant decrease overall is seen after intubation. Fig. 3 illustrates the distribution of individual changes in MAP before and after (within 1 h) in those who were intubated with propofol. Thirty seven percent (46/124) had a drop in MAP of greater than 10% soon after intubation, while 31% (38/124) had an increase in MAP of greater than 10%.

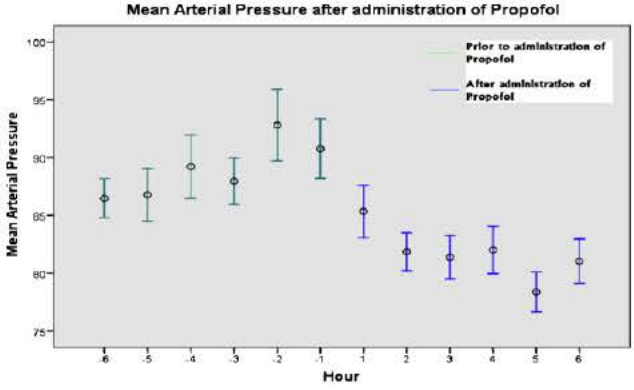

Fig. 2 – Mean arterial pressure after intubation with propofol (N = 124).

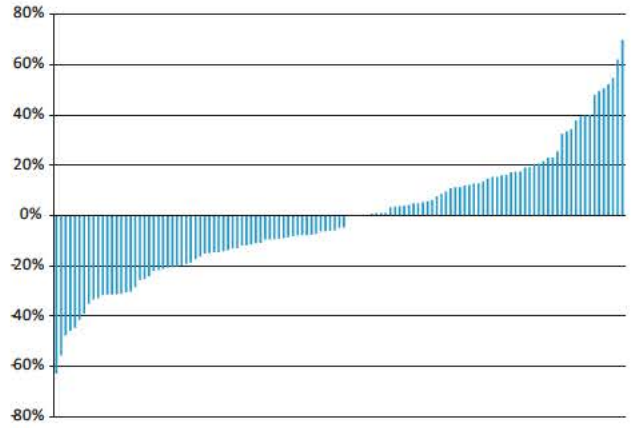

Fig. 3 – Percent change of mean arterial pressure after intubation with propofol (N = 124).

Table 2 – Outcome data for normotensive and hypotensive patients.

Effect	Point estimate	95% Wald confidence limits		*p* Value
% Total body surface area	1.016	1.004	1.027	<0.001
Presumed sepsis	1.852	1.100	3.117	0.02
Sepsis + propofol	1.071	0.377	3.043	0.34

With regard to our primary end point, clinically significant hypotension was seen in 117 (42%) of the total 279 intubations. Clinically significant hypotension was seen in 82 (49%) of the 168 intubations who had presumed sepsis, whereas only 35 (30%) of the 111 intubations who did not have concomitant presumed sepsis resulted in hypotension (*p* 0.004).

On multiple logistic regression, %TBSA [odds ratio (OR) 1.016, 95% confidence interval (CI) 1.004 1.027, $p < 0.001$] and the suspicion of sepsis (OR 1.852, 95% CI 1.100 3.117, *p* 0.02) were found to be the only significant predictors of hypotension. None of the induction agents, including propofol, were significantly associated with clinically significant hypotension in patients with or without presumed sepsis (see Table 2).

There was a significantly higher rate of death in the hypotensive group (*n* 117), with 32 (27.4%) patients dying compared to 28 (17.3%) to the group that did not experience hypotension (*n* 167) (OR 1.94, 95% CI 1.07 3.54; *p* 0.043). There was no significant correlation between hypotension and other secondary outcomes such as ICU days or ventilator days.

4. Discussion

This retrospective study revealed that use of induction agents, including propofol, was not a significant independent risk factor for the development of hypotension in the critically ill burned population following urgent endotracheal intubation. Multiple logistic regression showed that %TBSA burned and presumed sepsis were the only significant predictors of hypotension.

Previous studies have evaluated the airway management of burn patients as well as burn resuscitation. To our knowledge, this study is the first to examine the effects of specific induction agents used in critically ill burned patients, with a specific focus on propofol. The hypotensive effects of propofol are well known, and it is often implicated in post induction hypotension in critically ill patients. As early as 1994, physicians noted that propofol may decrease blood pressure enough to blunt the sympathetic response to laryngoscopy and tracheal intubation. During this time, Billard et al. investigated the interaction between propofol and fentanyl and the hemodynamic changes associated with varying concentrations of these agents used in succession, first fentanyl then propofol [6]. They performed a randomized controlled trial of 120 ASA I or II patients and found that using a propofol induction dose of 2 3.5 mg/kg creates the same degree of hypotension and that this hypotension was increased 2 fold when fentanyl in the concentration of either 2 or 4 mcg/kg was used prior to propofol introduction. They

also discovered that the maximum predicted propofol biophase concentration was achieved in all groups at 2.3 min, regardless of the dose of fentanyl, propofol, or both.

Reich et al. sought to establish statistically significantly multivariate predictors of hypotension within the 0 10 min following induction of anesthesia [7]. It was a retrospective study of 2962 patients undergoing general anesthesia with a primary endpoint of hypotension and secondary endpoint of adverse effect, mortality, and prolonged hospital stay. Induc tion agents included etomidate, propofol, thiopental, mid azolam, and fentanyl. It was found that 9% of patients suffered severe hypotension following induction, the majority in the 6 to 10 min timeframe ($p < 0.001$). Statistically significant predictors of post induction hypotension included ASA III or IV, baseline MAP <70 mmHg, age ≥50 years, the use of propofol, and increasing doses of fentanyl. Fentanyl was the only induction agent that showed a dose dependent effect on hypotension. Reich's study was important because it not only identified propofol as an independent risk factor for hypoten sion but also because it provided new data on the profound and negative impact of even a single severe hypotensive episode post induction. There is, in fact, a significant increase in mortality and prolonged hospital stay associated with clinical hypotension, exacerbated by the presence of ASA III status and age ≥65 years.

Although Ray et al. in 2010 also found evidence that even a single hypotensive episode post induction can lead to a significant increase in morbidity and mortality, they were not able to correlate this phenomenon to propofol [8]. Their study was a retrospective analysis of 176 patients intubated emergently for exploratory laparotomies and then recovered in the ICU. This group of investigators found that ASA status was the sole predictor for clinical hypotension. They also reported that as ASA status increased, physicians were more likely to use etomidate or ketamine/versed (p 0.001). All induction agents utilised roughly the same amount of steroids and/or vasopressor support during recovery in the ICU, with a trend toward the risk of hypotension or need for post intubation vasopressor usage being lower in the etomidate group.

It is well known that burn patients experience a 10 fold surge in catecholamines during their recovery phase preceded by a phase of heat induced superficial tissue damage, the recovery phase represents ischemia reperfusion injury relat ed to burn shock state and extensive intravenous fluid resuscitation. This process amounts to a subacute hyperdy namic and hypervolemic period of convalescence during which the sympathetic nervous system (SNS) works overtime to perfuse end organs. These recovering burn patients experience a huge increase in cardiac output for weeks to months, and the extent of this hyperdynamic state is highly associated with %TBSA burned, time since burn, the presence of edema, iatrogenic drug reactions, and severity of infection and inflammation. In the early 20th century, Haldor Sneeve proposed that burns would create a drop in cardiac output via an accumulation of blood in the splanchnic vessels [9]. This effect was from a shortage of circulating catecholamines after the surge of SNS activity in the recovery period of burns. Sneeve advocated providing adrenaline to replete the cate cholamine stores and recover blood pressure in these patients, since a hyperdynamic state is necessary to maintain adequate perfusion and heart filling in this shock state. It makes sense that propofol may have a dramatic and enhanced hypotensive effect in the burn patient since a known mechanism for this hypotension is inhibition of the SNS, upon which the burn patient is highly dependent. It also follows that hypotension would be enhanced in burn patients during the recovery period because they suffer from increased venous capacitance and subsequent hypotension from decreased splanchnic tone, which is an effect that propofol exerts in all patients, burned or not. Finally, it seems appropriate that propofol would have a heightened hypotensive affect in burn patients because they are, as described by Blalock in 1931 [10], massively edematous and thus by definition hypovolemic; and multiple studies, including Hoka's in 1998 [11], have associated hypovolemia with an exaggerated effect on propofol induced hypotension.

Since there is a glaring paucity of data on the effects of propofol induction on burn patients, Yamashita et al. sought to delineate a population pharmacokinetic formula for propofol in burn patients that would offer a patient specific infusion rate for sedation in the ICU during the SNS surge period [12]. He infused 17 burned patients and 19 non burned controls with 2 mg/kg propofol (the standard induction dose) and measured serum concentration up to 4.5 min after administration. He found that the increased volume of distribution typically seen in massive resuscitation and the enhanced rate of propofol clearance in burn patients led to a decreased serum propofol concentration despite dosing at standard induction or maintenance doses. A large part of this phenomenon relates to the fact that the surge in SNS increases hepatic blood flow from 20 to 35 mL/kg/min, thus increasing propofol clearance. Percentage TBSA and body weight were the two most significant covariates leading to clinical hypotension. Yamashita's work provides us data on the appropriate dose of propofol for maintenance of sedation in the ICU. Unfortunately, it is difficult to apply this data to bolus induction of propofol since the first 2 min of the study were not included in the data to allow for a primary mixing phase with incomplete distribution in central compartments. Little data is known about the effect of the induction of general anesthesia on hypotension in this context, as induction happens within 40 s of a propofol bolus, and this time period was discarded.

Based on the statistical analysis of the data, our study shows that potentially septic critically ill burned patients requiring intubation in the BICU, every 1% increase in %TBSA burned contributed to a 1.6% increase in the odds of the development of hypotension. This relation was entirely independent of any other existing factors, including the type of induction agent used, the presence of inhalational injury, and age. Additionally, if patients developed hypotension following endotracheal intubation, the odds of death in creased by nearly 2 fold.

This study has a few limitations inherent to retrospective studies. First, the definition of hypotension (within 1 h) could be seen as problematic, as post induction hypotension usually occurs immediately when it occurs. These data were difficult to extract accurately in a retrospective chart review of our electronic medical record. The best we could do was take the lowest blood pressure recorded during that hour and assume it

was the one immediately post intubation. Second, the hemodynamic response to any induction agent is typically dose dependant. We did not have consistent and accurate documentation of various dosages applied to analyze. Third, paralytics were used concomitantly with induction agents 54% of the time. This could have potentially affected our results. Fourth, we did not evaluate volume status peri intubation. This could be an important confounder that could affect our results. Additionally, our definition of 'presumed sepsis' can be seen as a major limitation as empiric antibiotics may have been initiated prematurely in those who were not truly septic and not started on those who may have been septic. This definition relies on the clinical judgment of the bedside clinicians and is rather subjective. We felt this definition to be a practical definition that could potentially be extrapolated to real life scenarios as it is unlikely that sepsis could be confirmed with 100% certainty at the time of emergent intubation in the BICU. It is possible that the odds of hypotension could be much higher in those with confirmed sepsis. A prospective trial with strict criteria perhaps based on the American Burn Association consensus conference definition of sepsis could potentially provide better clarity [13].

5. Conclusion

Our study provides compelling data that presumed sepsis and %TBSA are the key risk factors for the development of hypotension following intubation in critically ill burned patients; development of hypotension is associated with a near 2 fold increase in the odds of death. The use of propofol for the induction of anesthesia for endotracheal intubation in critically ill burned patients did not increase the odds of hypotension or death. In burn patients requiring emergent endotracheal intubation in the BICU, the care team should exercise caution in those with large burns and/or presumed sepsis. In these high risk patients, prophylactic measures should be taken to protect against clinically significant hypotension. A prospective study may be warranted to further evaluate the risk of certain induction agents used for emergent intubation in the BICU.

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