

Choice of General Anesthetics for Trauma Patients

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Abstract The trauma anesthesiologist has multiple competing concerns when supporting the patient with major trauma, but the priority must be focused on adequate resuscitation to facilitate surgical hemostasis. A broad, evidence-informed knowledge of airway management, resuscitation, physiology, pharmacology, and critical care is required to address the unique pathophysiological processes encountered in trauma. Judicious selection of anesthetic agents is crucial to ensure optimal outcomes. In this review, we describe approaches for the induction and maintenance of general anesthesia for the patient with major trauma. Considerations for ongoing resuscitation and hemodynamic instability will be explored and discussed with respect to the administration of anesthetic induction and maintenance agents. Practices at our institution are reviewed, including the administration of high-dose

opioids as an integral part of both resuscitation and anesthesia for the patient with major trauma.

Keywords Trauma anesthesia · General anesthesia for trauma · Trauma anesthesiology · Traumatic injury · General anesthesia · Anesthetic considerations

Introduction

The anesthesiologist's role while managing patients with major trauma is multi-faceted. Seriously injured patients often require damage control surgery (DCS), as well as damage control resuscitation (DCR), and many present with unknown or suboptimally managed pre-existing conditions [1]. A broad, evidence-informed knowledge of airway management, resuscitation, physiology, pharmacology, and critical care is required to address the unique pathophysiological processes observed in trauma [1]. In this review, we will describe approaches for the induction and maintenance of general anesthesia for patients with major trauma. Considerations for ongoing resuscitation and hemodynamic instability will be explored and discussed with respect to the administration of anesthetic induction and maintenance agents.

Induction Agents

Rapid sequence induction and intubation (RSII) is employed for newly admitted trauma patients using induction agents and neuromuscular blockers. A comprehensive review of RSII is beyond the scope of this review, but a brief overview is presented because these agents have important pharmacological and physiological effects in the severely injured trauma patient. For a thorough appraisal of RSII, the reader

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Table 1 Induction agents commonly used in trauma

Agent	Induction dose	Heart rate	Mean arterial pressure	Ventilatory drive	Bronchodilation	CBF	ICP	CMRO ₂
Thiopental ^b	1–3 mg/kg ^a	↑↑	↓↓	↓↓↓	↓	↓↓↓	↓↓↓	↓↓↓
Midazolam ^c	0.1–0.4 mg/kg	↑	↓↓	↓↓	0	↓↓	↓↓	↓↓
Ketamine	1–2 mg/kg	↑↑	↑↑	↓	↑↑	↑↑↑	↑	↑↑↑
Propofol	1–2.5 mg/kg ^a	0	↓↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓
Etomidate	0.2–0.3 mg/kg	0	↓	↓	0	↓↓↓	↓↓↓	↓↓↓
Remifentanyl	1 mcg/kg	↓↓	↓↓	↓↓↓	0	↓	↓	↓

CBF cerebral blood flow, ICP intracranial pressure, CMRO₂ cerebral metabolic rate of oxygen

^a Lower doses may be appropriate for hemodynamically unstable patients

^b No longer available in the United States

^c Onset of action when used as a sole agent for induction is excessively long (5 min); onset is faster when combined with opioids, but may still exceed 90 s

is referred to reviews by Stollings et al. [2•], and El-Orbany and Connolly [3•].

Neuromuscular blockers used for RSII in trauma patients include succinylcholine, rocuronium, and vecuronium. The depolarizing agent succinylcholine, at a dose of 1–2 mg/kg intravenously (3–4 mg/kg intramuscularly) is frequently the neuromuscular blocker of choice owing to its rapid onset (30 s) and short duration (5–10 min) [4]. In conditions where succinylcholine is contraindicated [2•, 4] or unavailable, the non-depolarizing neuromuscular blocker rocuronium (1 mg/kg) may be used [4]. Rocuronium has been shown to be as effective as succinylcholine in facilitating laryngoscopy during RSII [5, 6]. Administration of rocuronium (1 mg/kg) immediately prior to administration of propofol facilitates good to excellent intubating conditions within 60 s of dosing in non trauma patients, which is comparable to succinylcholine [4, 7]. There is limited data regarding the use of vecuronium for RSII, and this agent is not generally recommended due to a longer onset time (80–140 s), even when larger doses are used (0.3 mg/kg) [8–10]. However, despite limited data regarding vecuronium, during drug shortages, this agent may be considered as an alternative agent for neuromuscular blockade in RSII [2].

The induction agents most commonly used in trauma patients are etomidate, ketamine, and propofol. While each of these agents is useful for induction, the anesthesiologist must be knowledgeable about potential adverse effects. Other less commonly used agents described in the literature include remifentanyl, thiopental (no longer available in the United States), and midazolam [11•]. Induction agents used in trauma are summarized in Table 1.

Etomidate

Etomidate has been used extensively in the trauma population due to its rapid onset of action and neutral hemodynamic profile [12]. Etomidate is an imidazole-derived

sedative hypnotic that stimulates GABA receptors to block neuroexcitation and induce amnesia [2•]. Etomidate should be dosed based on ideal body weight in morbidly obese patients [2•]. Etomidate decreases CMRO₂, CBF, and ICP and is frequently used for induction of anesthesia in neurosurgery [13]. Etomidate helps maintain cerebral perfusion pressure, reduces CBF, and may be used for patients with traumatic brain injury (TBI). Side effects include myoclonus, pain on injection, and post-operative nausea, and vomiting. Etomidate cannot be administered intramuscularly, and therefore, is not useful in the combative patient when intravenous access has not been established. Despite its favorable hemodynamic profile, etomidate can cause arterial hypotension in the volume-depleted patient. Although the association between the use of a single dose of etomidate and mortality is inconclusive at this time [12], use of etomidate remains controversial in the critically ill because some studies have shown an association with increased mortality in patients with sepsis [14, 15]. Single dose etomidate use in the trauma population has also been associated with the increased rates of hospital-acquired pneumonia that may be attenuated with post-etomidate hydrocortisone therapy [16].

Ketamine

Ketamine, a dissociative agent, has a rapid onset of action when administered intravenously and may also be used intramuscularly in combative patients who do not have intravenous access. Ketamine is a lipophilic noncompetitive *N*-methyl-D-aspartic acid (NMDA) inhibitor with sites of action in the thalamocortical and limbic central nervous system [2•]. Ketamine indirectly increases cardiovascular stimulation through centrally mediated increased sympathetic tone and increased release of catecholamines; [13] hence, this agent is advantageous for maintaining adequate blood pressure in a hypovolemic patient [11•] and is a preferred induction agent in cardiac tamponade [4].

However, ketamine is also an direct myocardial depressant, and hypotension is possible in patients who are catecholamine depleted [2•]. Ketamine is useful in asthma and reactive airways disease for reducing bronchospasm associated with intubation [4, 13]. Use in TBI has been limited previously because of concerns for the increased ICP; yet, recent reviews on the topic have called into question that the evidence behind the proscription against use of ketamine in the head-injured patient [17–20]. In neurotrauma, ketamine may have neuroprotective properties [19•]. Furthermore, ketamine may help avoid hypotension—a variable in the initial phase of resuscitation that has been associated with poor outcomes in TBI [21].

Some investigations have linked peritraumatic use of the S (+) isomer of ketamine to an increased risk of acute stress disorder and post-traumatic stress disorder (PTSD) when compared to opioids [22]. The use of racemic ketamine (available in the United States) has been associated with an increased incidence of acute stress disorder including re-experiencing and hyper arousal, but has not been shown to contribute to PTSD [22, 23]. Consequently, data regarding the ketamine-PTSD relationship are inconsistent. In several other studies, ketamine has been shown to have antidepressant properties [24, 25] and is currently being evaluated as a treatment for PTSD (<http://clinicaltrials.gov/show/NCT00749203>). Institutional dispensing, tracking, and documentation procedures may place barriers to the timely access and use of ketamine compared to other induction agents.

Propofol

Propofol is a widely used sedative hypnotic that has been adapted for use by experienced anesthesia practitioners in trauma patients even though evidence regarding outcomes in this population is lacking. Propofol has the advantage of familiarity, rapid onset, profound amnesia, short duration of action, blunting of the sympathetic outflow during laryngoscopy and intensification of muscle relaxation [11•]. This agent is highly lipid-soluble and acts as a GABA agonist. Propofol decreases CMRO₂, CBF, and ICP, making this a preferred agent for hemodynamically stable TBI patients [26]. Propofol reduces systemic vascular resistance, has myocardial depressant effects, and therefore, must be used with extreme caution in patients with the potential for hemodynamic instability. Reduced dosing alone in hypovolemic patients may not be sufficient to maintain adequate mean arterial pressure and cerebral perfusion pressure. Our institutional practice is to use reduced doses of propofol in patients with the potential for hemodynamic instability (0.5–1 mg/kg or lower) with adjunctive use of intermittently dosed phenylephrine (100 mcg intravenous boluses) to maintain mean arterial

pressure in hypovolemic patients. A ketamine/propofol admixture (ketamine 0.75 mg/kg; propofol 1.5 mg/kg) has been studied and found to improve post induction mean arterial pressure in the non trauma patient compared to propofol (2 mg/kg) alone [27].

Adjuncts

During RSII, additional agents have been traditionally used to attenuate additional negative physiological responses that may occur during intubation [2•]. Lidocaine has been proposed as an agent that may prevent increases in ICP in TBI patients, especially when succinylcholine is administered. However, the mechanism is incompletely understood and several reports have refuted any potential beneficial effects in TBI patients [28]. Moreover, in at least one study, lidocaine administration was associated with decreased blood pressure when administered for RSII [2•, 29]. ICP does not reliably decrease with lidocaine, and a number of studies have demonstrated elevation of ICP when this agent is bloused [2•, 30]. If used, a typical dose is 1.0–1.5 mg/kg, given intravenously 2–3 min before RSII. Atropine is another adjunct to consider, especially in pediatric patients or in patients with increased vagal tone. When indicated in adults at risk for bradycardia during RSII (i.e., patients on beta-blockers, amiodarone, calcium channel blockers, and digoxin) a dose of 0.01 mg/kg is recommended [2•].

Maintenance of General Anesthesia

Earning the Anesthetic

Resuscitation is the primary intraoperative role for the anesthesiologist during DCS for the patient with major trauma. Hence, patients “earn an anesthetic” once hemodynamic stability has been achieved. It is imperative for the trauma anesthesiologist to be aware of the patient’s injuries before anesthetic agents are indiscriminately titrated. There may be a significant amount of bleeding into the retroperitoneum from a severe pelvic injury or bleeding into compartments due to bilateral femur fractures requiring resuscitation in volumes not anticipated. Trauma patients in compensated or decompensated shock have a much lower volume of distribution for all anesthetic agents and these must be adjusted accordingly. If the patient has a positive focused abdominal sonogram for trauma (FAST) exam with a suspected tense peritoneum, high-dose opioid loading should be delayed until surgical hemostasis has been achieved. DCR is carried out in a high blood product ratio-driven manner while maintaining systolic blood pressure greater than 90 mmHg systolic or a mean arterial

pressure of greater than 50 mmHg in the patient without TBI [31, 32]. In patients who remain severely hypotensive during DCR, there may not be an opportunity to administer any additional anesthetic agents.

Induction and maintenance of anesthesia may produce profound hypotension and/or cardiac arrest in major trauma, and anesthesiologists should be familiar with alternative amnestic agents. Both induction agents and volatile anesthetics have a dose-dependent negative effect on hemodynamic stability due to vasodilation. Thus, it may be challenging for the anesthesiologist to provide amnesia for victims of major trauma. Awareness is a rare complication during general anesthesia with a reported prevalence of 0.1–0.2 % in adults undergoing elective surgery, but the prevalence is higher in major trauma cases when the patient is too hemodynamically unstable to tolerate anesthesia [33, 34]. Patients who experience awareness under anesthesia may develop serious long-term consequences such as PTSD [35].

Benzodiazepines are a class of drugs that provide amnesia but do not cause vasodilation, and thus can be used in hemodynamically unstable patients. These agents can reduce the incidence of awareness during resuscitation until additional anesthesia can be given [34]. Scopolamine, an anticholinergic amnestic, has historically been touted as an effective agent to prevent intraoperative awareness, although data regarding the dosing and effectiveness in trauma are sparse [36]. Based on a 2006 Practice Advisory, either benzodiazepines or scopolamine may be considered on a case-by-case basis for selected patients, including trauma patients who may require smaller doses of anesthetics [37]. Our institutional practice is to administer intravenous midazolam (2–4 mg) or diazepam (5–10 mg) if the patient is too unstable to tolerate volatile anesthetics and deemed to be at risk for intraoperative awareness. An anecdotally endorsed dose for intravenous scopolamine is a single administration of 0.2 mg. Scopolamine must be used with caution in patients with TBI because this agent has a long half-life (4.5 h) and can confound subsequent neurological examinations (i.e., pupillary dilatation).

Volatile Anesthetics: Effects in the Trauma Patient

Volatile anesthetics such as desflurane, isoflurane, and sevoflurane have been identified as effective modulators of the inflammatory response in various states of tissue injury, exerting beneficial effects on organ function and overall outcome in both animal [38–41] and human models [42–44]. Most previous studies elucidating the protective potential of volatile anesthetics have focused on ischemia–reperfusion injury and biomarkers of organ injury rather than clinical outcomes [45]. Although volatile anesthetics are often used as anesthetic agents during the initial

anesthesia for surgery for major trauma, the effect of these agents on the inflammatory response, coagulation system, and outcomes of trauma patients is unknown. At our institution, as blood pressure improves to greater than 90 mmHg systolic, inhalation agents are increased to half minimum alveolar concentration (MAC) or greater. In patients with severe TBI, volatiles are normally titrated to less than 1 MAC to avoid dose dependent increases in CBF and ICP. Vigilance when administering volatile anesthetics is imperative because the patient's clinical condition may rapidly change, especially if missed injuries are encountered during or after DCR and DCS. There are no quality data to support preferential selection of one volatile agent over others in trauma patients. In patients with multiple injuries and multiple episodes of severe hemodynamic instability, volatile agents with lower blood-gas partition coefficients are generally selected (i.e., sevoflurane or desflurane) to permit rapid titration. At our institution, we generally avoid nitrous oxide in trauma patients for several reasons. First, nitrous oxide expands all gas spaces and can worsen pneumothoraces, pneumocephalus, small bowel obstructions, and expand endotracheal tube cuffs. Second, nitrous decreases hypoxic drive, increases pulmonary vascular resistance, and can cause diffusion hypoxia [46, 47]. In patients with TBI, nitrous oxide increases CMRO₂ and ICP and may disturb cerebral blood flow-CMRO₂ coupling [46]. Finally, there is evidence that nitrous may alter immunological responses to infection, cause apoptosis, increase homocysteine levels, and mask myocardial depression [47, 48] (Fig. 1).

Titration of High-Dose Opioids

The return of adequate micro-circulatory flow is the ultimate goal of trauma resuscitation [49]. After the control of acute hemorrhage, ongoing resuscitation continues using warmed blood components administered at high ratios with correction of electrolytes [50]. The correction of acid–base derangements is accomplished with adequate resuscitation and not pharmacologic correction (i.e., sodium bicarbonate [51] and vasopressors). The result of this continued resuscitation is an increasing systolic blood pressure. An increase in systolic blood pressure is an indicator of increasing macro-circulatory pressure, but this does not necessarily indicate an increase in macro or micro-circulatory flow. As the blood pressure continues to rise, fentanyl may be added to the anesthetic regimen in order to begin dilating the microcirculation. In our practice, we begin with 50–150 mcg doses of intravenous fentanyl and observe the physiologic response. If there is a reduction in blood pressure, the resuscitation is continued until there is a positive response with return of blood pressure to the systolic target (>90 mmHg). Hypotension following

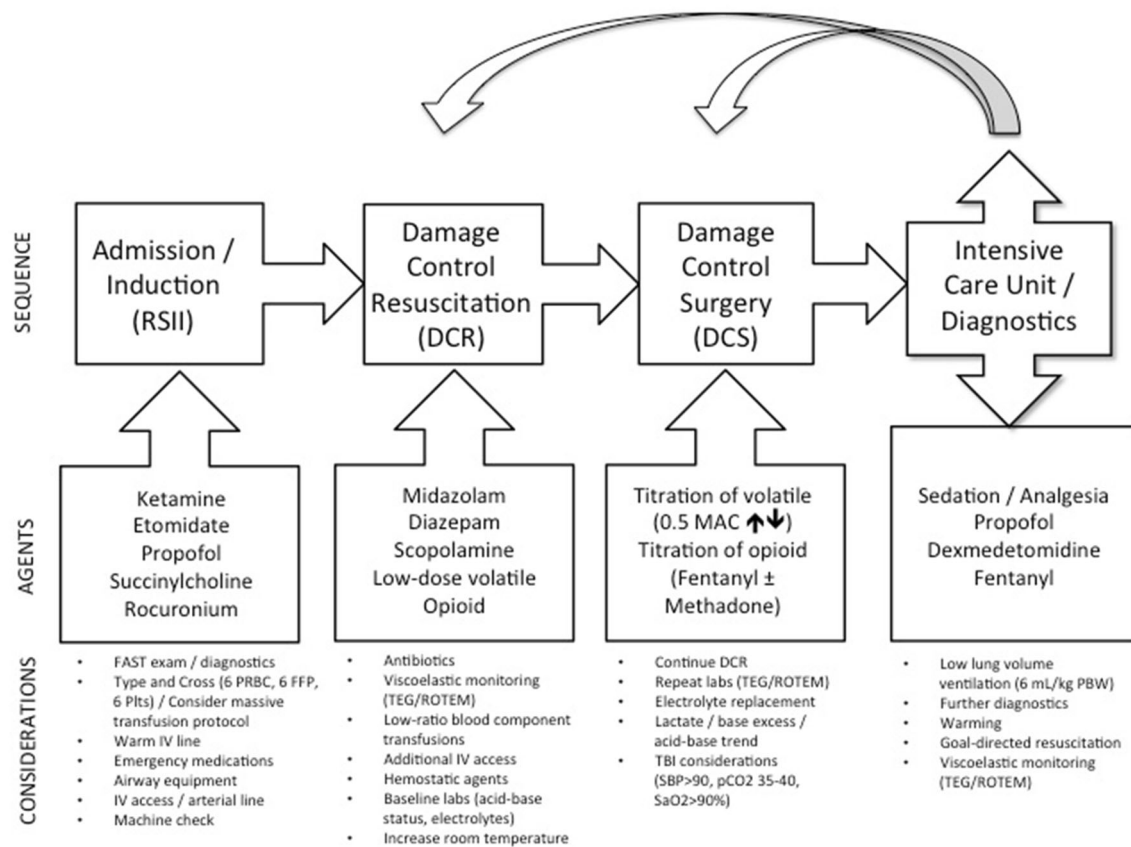


Fig. 1 Overview of anesthetic considerations during damage control resuscitation (DCR) and damage control surgery (DCS) [64•, 65•]

increased MAC or doses of opioid may be an indication of a reduction in vascular tone. As this response becomes minimal with subsequent doses of fentanyl, the dose is increased in a stepwise fashion. This dose-response is continued until the patient tolerates a single bolus of approximately 250 mcg of fentanyl. In most cases the patient will receive a total dose of 20–30 mcg per kilogram or more of fentanyl. It must be remembered that the patient's estimated blood volume is constantly changing during the resuscitation, as is the plasma level of the dosed opioid. The dose is ultimately determined by the physiologic response of the patient following administration of the opioid and titration of other anesthetic agents.

If there is no longer a response to fentanyl while goal-directed resuscitation continues, and there is still evidence of tissue hypoperfusion as evidenced by an elevated lactate and base deficit, our institutional practice is to add an additional opioid such as intravenous methadone in 10 mg increments to a maximum dose of 20–30 mg if the patient's QTc is within normal limits (<440 ms). The addition of methadone causes additional vasodilatation and may require additional resuscitation. This high-dose opioid-resuscitation method can only be carried out if the patient's perfusion pressure is adequate

and hemorrhage control assured. The addition of methadone may help blunt the catecholamine response until arrival at the intensive care unit or radiology suite. When methadone is contraindicated, an alternative opioid for titration is hydromorphone, titrated in 0.2–0.4 mg increments to a total dose of 2 or more mg for the case. Morphine is generally avoided in our practice due to concerns about histamine release, which may exacerbate hypotension.

It must be noted that this high-dose opioid anesthetic technique has not been previously described with such detail in the literature, but has been the mainstay of the anesthetic technique combined with intraoperative resuscitation at the R Adams Cowley Shock Trauma center for many years. Trauma anesthesiologists at our institution have speculated that administration of high doses of opioids may improve tissue perfusion [52•], though in vivo evidence to support this theory is lacking. Opioids may blunt deleterious activation of the sympathetic nervous system and alter microcirculation in a way that may prevent further tissue damage in hemorrhagic shock. It has been shown that high levels of catecholamines are associated with an increase in biomarkers that indicate endothelial damage, glycocalyx breakdown [53] and

perpetuation of hyper fibrinolysis [53, 54]. Biomarkers related to ongoing catecholamine release are also related to coagulopathy, which increases mortality [55, 56]. Restoration of adequate micro-circulatory blood flow is crucial in shock reversal, as well as protection of the endothelial glycocalyx. This is essential in order to minimize leukocyte-endothelial interaction, as well as maintaining the integrity of the vascular basement membrane [49, 57]. As the lactate and base deficit normalize and the vasodilatory response to the opioid becomes minimal, two central, but unequivocally essential resuscitation goals are achieved: return of micro-circulatory flow and the correction of the acute coagulopathy of trauma, and blunting of the catecholamine response.

Several studies have documented the beneficial role of opioid receptor agonists in hemorrhagic shock [52, 58, 60]. In various animal studies, opioids have been shown to precondition skeletal and myocardial tissue, [58, 59] promote hemodynamic recovery [62], and provide protection against acute ischemia [61]. Morphine has been shown to attenuate microvascular hyperpermeability after hemorrhagic shock, possibly due to dependence on protein kinase A [62]. Retrospective studies are planned using data from the recently completed pragmatic randomized optimal platelet and plasma ratios (PROPPR) [63] to help elucidate the impact of opioid dosing on the inflammatory response and coagulation abnormalities in patients with severe trauma who require massive transfusion. Further prospective in vivo investigations are indicated to establish the mechanism, physiological effects, and outcomes associated with a high-dose opioid anesthetic approach for patients with major trauma.

Conclusion

The trauma anesthesiologist has multiple competing concerns when supporting the patient with major trauma, but first and foremost, adequate resuscitation must be assured to enable surgical hemostasis. Judicious selection of anesthetic agents is crucial when supporting the physiology of the severely injured trauma patient. Future studies are warranted to evaluate the effect of different anesthetic regimens on physiological endpoints and clinical outcomes.

Compliance with Ethics Guidelines

Conflict of Interest Robert A. Sikorski has received honoraria from Edwards Lifesciences for various lectures on hemodynamic monitoring and resuscitation. A. Ken Koerner declares that he has no conflict of interest. L. Yvette Fouche-Weber declares that she has no conflict of interest. Samuel M. Galvagno, Jr. declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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