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REVIEW ARTICLE

Anaesthesia in haemodynamically compromised emergency patients: does ketamine represent the best choice of induction agent?

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Summary

In rapid sequence induction of anaesthesia in the emergency setting in shocked or hypotensive patients (e.g. ruptured abdominal aortic aneurysm, polytrauma or septic shock), prior resuscitation is often suboptimal and comorbidities (particularly cardiovascular) may be extensive. The induction agents with the most favourable pharmacological properties conferring haemodynamic stability appear to be ketamine and etomidate. However, etomidate has been withdrawn from use in some countries and impairs steroidogenesis. Ketamine has been traditionally contra-indicated in the presence of brain injury, but we argue in this review that any adverse effects of the drug on intracranial pressure or cerebral blood flow are in fact attenuated or reversed by controlled ventilation, subsequent anaesthesia and the greater general haemodynamic stability conferred by the drug. Ketamine represents a very rational choice for rapid sequence induction in haemodynamically compromised patients.

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Rapid sequence induction (RSI) of anaesthesia is an appropriate technique in situations where a patient needs emergency surgery. Such patients are also frequently haemodynamically compromised (acutely or chronically), suboptimally resuscitated and/or suffer extensive various comorbidities. Typical scenarios might include ruptured abdominal aortic aneurysm, septic shock secondary to pneumonia, or polytrauma. The key attributes of RSI are purported to be rapid onset of anaesthesia using a predetermined dose of induction agent (since there is no time to titrate dose to effect), use of a rapid-onset neuromuscular blocking agent (such as suxamethonium) to provide optimal tracheal intubating conditions, and an airway 'rescue plan', to implement if tracheal intubation should fail [1].

Beyond the anatomical considerations that determine the success of tracheal intubation, the overall success of RSI is also dependent on the appropriate selection of induction agent and neuromuscular blocking agent. In this article we focus on the former (readers are referred to other sources for a discussion of the latter) [2]. The pharmacological properties required of an intravenous induction agent that satisfy the aims of RSI therefore include rapid onset and few adverse (i.e. haemodynamic) effects.

Pharmacokinetics and pharmacodynamics in shocked patients

Intravenous anaesthetics are presumed to exert their ultimate effects by action at some unknown central nervous system site(s) – the hypothetical 'effector site(s)'. The speed with which they act here can be modeled using pharmacokinetic principles. In RSI, the predetermined dose of agent must be sufficient to ensure lack of awareness during tracheal intubation and to facilitate

prompt commencement of surgery. Theoretically, any drug will work quickly if a large enough bolus dose is administered but the larger the induction bolus dose, the greater will be the incidence and magnitude of any adverse (haemodynamic) effects. The effector site *equilibration constant* (K_{eo}), represents the time taken for the administered agent to reach an appropriate (anaesthetic) *concentration* at the hypothetical site in the brain (C_e). More conventionally, the *half-life* ($t_{1/2}K_{eo}$) of this inverse exponential process is quoted. Various models exist to determine these constants (e.g. analysis from arteriovenous concentration gradients using the Fick principle, or observation of clinical effects coupled with electroencephalographic changes) [3]. Thus, rapid induction *can* be performed with propofol ($t_{1/2}K_{eo}$ up to 20 min) *but* a high initial plasma concentration is required to ensure cerebral transfer, and thus higher relative injected bolus dose is necessary. Hence intravenous anaesthetic agents with the shortest $t_{1/2}K_{eo}$ are generally best suited to the non-titrated use in RSI (Table 1). Consistent with this notion, a study using ketamine 1.5 mg.kg^{-1} vs thiopentone 4 mg.kg^{-1} in obstetric practice (RSI with rocuronium 0.6 mg.kg^{-1}) reported satisfactory conditions for early intubation (45 s) in all cases in ketamine, while thiopentone caused difficulty in 75% of cases [5].

In general shocked patients manifest a greater haemodynamic and nervous system sensitivity to anaesthetic agents. While many clinicians intuitively reduce induction agent doses in shock to reduce adverse effects, awareness is well recognised during emergency anaesthesia, often as a consequence of dose reduction. Conversely, a 'blood-brain circuit' often exists in shocked patients which paradoxically delivers the required brain C_e. Furthermore, many anaesthetic agents exhibit high protein binding: in severe hypovolaemic shock, especially after fluid resuscitation, the non-protein bound, free fraction of drug is increased which achieves C_e despite reduced dose and increases adverse haemodynamic effects of the drug. Therefore, in haemodynamically compromised patients there are complex pharmacokinetic and dynamic interactions, which can increase or decrease the efficacy and adverse effects of intravenous anaesthetic agents. Predicting the response (i.e. underdosing and awareness vs haemodynamic collapse) in any one patient is challenging, which favours agents which require minimal dose reduction and high therapeutic index (i.e. safety margin).

The available induction agents

The 'ideal' emergency anaesthetic induction agent is one which rapidly achieves unconsciousness and yet does not itself cause haemodynamic compromise (Table 1). One philosophy is to argue that in certain circumstances, any induction of anaesthesia is too hazardous. The obtunded patient is assumed to be sufficiently unconscious to allow surgery to progress without the need for any anaesthetic agent (with its attendant side-effects). However, in practice emergency (and cardiac) anaesthesia are well-documented to be associated with an increased incidence of awareness [6]. Ketamine induction followed by appropriate maintenance with a volatile agent yielded awareness under anaesthesia in ~11% of trauma cases (itself a high incidence), compared with ~43% recall

Table 1 Pharmacological properties of commonly available intravenous induction agents (adapted from Pandit [4]).

Intravenous induction agent	Effector site equilibration and $t_{1/2}K_{eo}$	Haemodynamic effects in vivo	Comments and idiosyncratic reactions (see text)
Ketamine	Undetermined (see text), but probably ~2 min	↑CO, ↑HR, ↑ABP Sympathomimetic	→ or ↑CPP and →ICP with standard anaesthetic management
Thiopentone	1.5 min	↑HR, →CO, ↓ABP →laryngeal reflexes, ↓inotrope, vasodilates	Haemodynamically compromised patients unlikely to tolerate induction dose > 3 mg.kg^{-1}
Propofol	≤20 min	→HR, ↓CO, ↓ABP Vagotonic, ↓laryngeal reflexes	Haemodynamic compromise marked in elderly, ASA 3 or more or hypovolaemic patients with 'standard' induction dose
Etomidate	~2.5 min	→CO, →ABP Minimal dose adjustment in shock	Prolonged inhibition of steroid synthesis in the critically ill; withdrawn from number of countries
Benzodiazepenes	~9 min (e.g. lorazepam)	→CO, →HR	Induction time of anaesthesia incompatible with RSI
Phenylpiperidenes	~6 min (e.g. fentanyl)	Vagotonic, ↓CO, ↓HR, ↓ABP Vagotonic, ↓laryngeal reflexes	Potent vagally mediated bradycardia can compound effects of hypovolaemia

CO, cardiac output; ABP, arterial blood pressure; HR, heart rate; CPP, cerebral perfusion pressure; ICP, intracranial pressure.
ASA, American Society of Anesthesiologists preoperative grade.
↑, Increased; ↓, decreased; →, unaffected.

where no anaesthetic agent was administered (which is extremely high) [7, 8]. In emergency obstetric surgery, concerns for the fetus and the risk of haemodynamic compromise with high doses of induction agent historically led to anaesthetic techniques which minimised induction doses and consequently were associated with high rates of awareness under anaesthesia [9, 10].

Of the available agents (Table 1), etomidate remains a very popular choice for haemodynamically compromised patients as it generally helps maintain haemodynamic stability [11, 12]. In an animal model of haemorrhagic shock, almost no dose reduction in etomidate was required as compared with non-shocked animals to achieve the same clinical effect [13]. A rat model demonstrated $t_{1/2}K_{eo}$ ~2.7 min (control) and 2.3 min (hypovolaemic), indicating that shock had little effect on the ability of etomidate to reach the effector site in an acceptable time [14]. Etomidate tends to preserve the pressor response to laryngoscopy, and this also helps preserve haemodynamics [15]. However, etomidate has been withdrawn from use in a number of countries due to concerns that its prolonged use impairs endogenous steroid synthesis in the critically ill [16–18]. The recent 'CORTICUS' study confirmed that steroid suppression occurred in 60% of septic patients who received etomidate compared with 43% who did not, an effect that can persist up to 67 h, indicating that the adverse effects are possibly important even a single bolus dose [19].

Propofol is perhaps the most popular intravenous induction agent in the developed world for *elective* cases, but objective descriptions of its use and safety in *shocked or emergency* patients are sparse. In a porcine model of haemorrhagic shock followed by crystalloid resuscitation, brain concentrations of the drug were much higher than controls when equal doses were administered, indicating that much lower doses are likely needed in shock (and that perhaps some mechanisms concentrate the drug in the brain when systemic vascular pressures are low) [20, 21]. Therefore, some workers suggest reducing the propofol dose to 10–20% of a 'healthy patient' dose (i.e. reduce the dose from 1–2 $mg.kg^{-1}$ which is standard in elective surgery, to ~0.1–0.4 $mg.kg^{-1}$ in shocked patients) and also coupling this with a slow administration (e.g. injection over ~10 min) [22]. If this timescale is optimal to minimise haemodynamic compromise it is not compatible with RSI. Furthermore propofol's long $t_{1/2}$ K_{eo} (up to 20 min) means that risk of awareness during induction/tracheal intubation is high. Shafer and Reich et al. suggest that: *'alternatives to propofol anesthetic induction [should be] considered in patients > 50 years of age with ASA physical status ≥ 3… It is advisable to avoid propofol induction in patients who present with baseline blood pressure < 70 mmHg.'* [23] and *'propofol is particularly poor choice for induction of anaesthesia in patients with shock even after resuscitation'* [22].

Barbiturates (e.g. thiopentone) possess many desirable properties as sole induction agents: a short $t_{1/2}K_{eo}$ of just ~1.5 min a tendency to preserve autonomic responsiveness (e.g. reflex tachycardia and pressor response to laryngoscopy). However arteriolar vasodilatation, negative inotropy and obtunded baroreceptor responses make barbiturates less convincing a choice in patients with severe haemodynamic compromise, and in such circumstances significant reduction in arterial pressure is observed [24]. Shocked patients rarely tolerate higher doses of thiopentone (~5 $mg.kg^{-1}$). Polypharmacy – typically the combination of a phenylpiperidene and thiopentone – exacerbates hypotension by a vagally-induced suppression of compensatory tachycardia.

A so-called 'cardiac anaesthetic technique' consists of relatively high dose phenylpiperidene opioid combined with a low dose of intravenous anaesthetic agent along with with a neuromuscular blocking drug. The cocktail of drugs is purported to promote haemodynamic stability in patients undergoing surgery for valvular or coronary artery disease. While this may be true of medically optimised elective patients, instability may result in emergency surgery in shocked/hypovolaemic patients [25–27]. In an emergency department setting, comparison of thiopentone, midazolam and fentanyl for RSI confirmed patients with pre-existing haemodynamic compromise (pulmonary oedema, sepsis, intracranial haemorrhage), 24% developed significant hypotension during RSI [24]. In this regard the various agents showed no significant differences and mortality was identical between groups, although this study was underpowered to detect the latter. Using fentanyl as the sole agent for induction of 'anaesthesia' may not prevent awareness, even when combined with nitrous oxide [28, 29].

Large doses of benzodiazepines can theoretically be used to induce anaesthesia, but this is of little practical value in RSI. Midazolam demonstrates 95% protein binding, inhibiting entry into the brain effector sites and the half life for closure of its imidazole ring which enhances lipid solubility and brain entry is a very long 10 min (for lorazepam ~9 min [30]) making these agents almost useless for RSI.

Pharmacological properties of ketamine relevant to RSI

The pharmacological properties of ketamine are well described elsewhere [31, 32]. Racemic ketamine is highly lipid soluble with a pK_a of 7.5, almost 50% dissociated at pH 7.45, and only 12% bound to plasma proteins. These properties ensure rapid blood-brain equilibration and

clinical onset which are well suited to use in RSI. Rat models using cerebral distribution kinetics demonstrate $t_{1/2}K_{eo}$ of just ~2 min [3]. In this article all doses refer to the racemic mixture and a typical RSI dose (~1.5 mg.kg^{-1}) produces plasma levels ~2 mg.ml^{-1} with 'awakening' occurs at plasma levels of ~500–1000 ng.ml^{-1}. While beyond the scope of this article, ketamine is well suited to maintenance anaesthesia and in a swine model of haemorrhagic shock and resuscitation, ketamine total intravenous anaesthesia produced significantly less hypotension than isoflurane [33].

Animal models can be used to demonstrate toxicity using the LD50 (median lethal drug dose), the ED50 (median effective dose) and the therapeutic index (the ratio LD50/ED50). Although values vary between species, in primates the therapeutic index for ketamine is 16 as compared with thiopentone of ~7 [34]. Thus, in human-like species, ketamine is, crudely, twice as 'safe' as thiopentone.

The direct effect of ketamine on the heart is negatively inotropic, especially in heart failure [35]. However, in vivo with an intact autonomic nervous system, ketamine acts as a sympathomimetic to increase heart rate, arterial pressure, and cardiac output [36, 37]. Furthermore, there is preservation of baroreflex responses [38]. In animal models of endotoxin induced shock, ketamine preserves mean arterial pressure, prevents metabolic acidosis and cytokine responses in a dose dependent fashion [39]. The combination of rapid blood-cerebral transfer kinetics, sympathomimetic haemodynamic effects, and absence of idiosyncratic adverse effects (especially impaired steroidogenesis such as occurs with etomidate) all confer distinct advantages on ketamine when used for RSI in haemodynamically compromised patients.

Ketamine in the context of brain injury

Ketamine is argued by some authorities to be contraindicated in the presence of traumatic brain injury, as it might elevate intracranial pressure (ICP) [40]. Elevated ICP could impair cerebral blood flow (CBF) according to the relationship:

$$\mathrm{CPP} = \mathrm{MAP} - (\mathrm{ICP} + \mathrm{CVP})$$

where CPP = cerebral perfusion pressure, MAP = mean arterial pressure, and CVP = central venous pressure.

So ketamine would not *seem* desirable in the context of brain trauma, where it might reduce CBF. However, following brain injury, cerebral autoregulation is impaired and CBF is essentially pressure (CPP) related, and thus an agent which maintains systemic haemodynamic stability will maintain CBF. Furthermore, following polytrauma, brain injury and shock co-exist; the latter will reduce CBF, so an agent such as ketamine which preserves systemic blood pressure maintains CBF. Early work suggested ketamine increased CBF via cerebral vasodilatation during spontaneous ventilation, but any adverse effects of ketamine in increasing ICP are avoided by controlled ventilation and subsequent sedation [41, 42]. Furthermore, ketamine reduces cerebral oxygen consumption ($CMRO_2$) and so the overall balance of CBF and $CMRO_2$ in the presence of ketamine is favourable [43–45].

Despite widespread avoidance of ketamine by clinicians following (actual or potential) brain injury, this stance does not withstand scrutiny and we would argue that ketamine is a rational choice for use in patients with brain injury, especially where haemodynamic compromise (e.g. polytrauma) is present or likely [46].

Evidence supporting ketamine use in haemodynamically compromised patients

We conducted a formal literature search of the literature using relevant search terms. This retrieved > 10 000 citations using the single search term 'ketamine', but only two of these were human clinical trials in the context of RSI [5, 47]. Thus there appears huge disparity between the ubiquity of RSI performed daily worldwide, and its (under)representation in the literature. This may be because ketamine is most commonly used in the developing world [48] or in warfare, and these settings are relatively rarely compatible with clinical trials.

We have summarised key references on the clinical use of ketamine in Table 2: of the > 10 000 articles retrieved, only the 12 studies quoted make meaningful comment (with supporting evidence) on the use of ketamine in RSI in situations of haemodynamic compromise, and only two of these directly compared ketamine with another agent [5, 47]. In emergency surgical patients ketamine increased mean arterial pressure by a mean of 10% and White concluded that it thus *'[offers] an advantage over thiopental in situations where hemodynamic stability is crucial'* [47]. In obstetric RSI (with rocuronium as neuromuscular blocker), ketamine enabled earlier (by ~45 s) and easier tracheal intubation than thiopentone [5].

Endorsement of ketamine by healthcare organisations

Although the current objective evidence base from clinical trials in favour of ketamine may not be overwhelming, it is notable that a number of organisations involved in delivering care to victims of trauma or in conflict situations, especially in the developing world

Table 2 Summary of relevant clinical studies using ketamine. 'Resource poor' refers to developing world and conflict settings, or other remote situations with no piped gas supplies and minimal monitoring.

Study	Clinical setting	Nature of publication	Principal finding/conclusion
Baraka et al. [5]	Resource poor obstetrics	Randomised trial of ketamine vs thiopentone in resource poor obstetric setting	Favors ketamine to thiopentone (end-point was intubating condition; rocuronium used as neuromuscular blocking agent)
White [47]	Emergency surgery	Randomised trial of thiopentone vs ketamine	Superior haemodynamics with ketamine (and emergence phenomena prevented by co-administration of midazolam)
Craven [48]	Resource poor	Review	Favours ketamine for hypovolaemic shock
Pesonen [49]	Resource poor	Case series (65 cases)	Low incidence of hypoxia breathing room air with ketamine anaesthesia
Magabeola [50]	Resource poor	Case series (135 cases)	Satisfactory increase in BP with ketamine (co-administration of atropine)
Porter [51]	Pre-hospital, non-anaesthetist use	Case series (32 cases)	Satisfactory use of ketamine for extricating trauma victims and providing analgesia while maintaining spontaneous breathing
Bonnanno [52]	Resource poor	Case series (62 cases)	Satisfactory use of ketamine with minimal monitoring available
Gofrit et al. [53]	Pre-hospital/conflict, non-anaesthetist use	Pilot study in trauma	Satisfactory use of ketamine in restless patients with trismus
Mulvey et al. [54]	Resource poor	Case series (149 cases)	Strongly advocates ketamine as first-line induction agent in disaster area surgery
Mellor [55]	Resource poor	Review	Favors use of ketamine especially for non-physician use
Meo et al. [56]	Resource poor	Review	Favors use of ketamine including emergency surgery
Wood [57]	Pre and in-hospital trauma	Review	Favors ketamine for trauma

feel able to recommend ketamine as a first-line agent for anaesthetic induction. These are embedded in the 'in-house' manuals or guides of these institutions, and also some studies in Table 2 were sponsored or conducted by some of these agencies. These bodies include the International Committee of the Red Cross and the Finnish Red Cross (who advocate ketamine anaesthesia for both induction and maintenance during surgery in field hospitals [49], Table 2), the West Midlands Ambulance Service and British Association for Immediate Care (who recommend it for non-physician pre-hospital procedural sedation and anaesthesia [51], Table 2), the Italian Comitato Collaborazione Medica (who advocate it for emergency anaesthesia in field hospitals [56], Table 2), and the Motorcycle Union of Ireland Medical Team (MUIMT) who use only ketamine for pre-hospital trauma RSI (personal communication Dr John Hind, Medical Officer MUIMT). When the Association of Anaesthetists of Great Britain and Ireland commissioned a special 'developing world' supplement to *Anaesthesia*, ketamine featured as the key induction agent in this setting [48].

Developing the evidence base: future research

The lack of evidence concerning ketamine may be compounded by perhaps 'negative attitudes' to the drug within the profession. Trainees are rarely taught formally to use it (e.g. it does not appear explicitly in competency-based training schedules of the Royal College of Anaesthetists [58]. There is possibly a perception that it is somehow an inferior agent of only historical interest. The lack of training in its use becomes a self-fulfilling prophecy: many practitioners are currently probably unfamiliar with managing dissociative anesthesia using ketamine and so unable to train others in its use.

A clinical trial assessing induction agents in haemodynamically compromised patients would undoubtedly help inform clinical practice. A study enrolling emergency or trauma cases into a single drug-intervention trial is just as crucial as other 'megatrials' and would likely be similar in structure [59]. It is unfortunate that such trials are sparse if not absent from the anaesthetic literature, in contrast to other specialties such as cardiology e.g. where the landmark International Study of Infarct Survival (ISIS II and III) established thrombolysis as routine practice for a single drug bolus therapy in an acute setting) [60, 61]. While we are also interested in outcome from a bolus injection of a single drug in an acute setting, perhaps the most challenging aspect of any future trial will be its primary end point. Arterial blood pressure is the most immediately measured and perhaps most widely used variable in clinical practice. The SHRED study demonstrated how randomisation of a relatively small number of patients (86 patients randomised between three drugs) can satisfactorily identify significant haemodynamic differences between groups based on blood pressure [24]. However, arterial pressure provides only a snapshot of the

haemodynamic state, and other aspects such as cardiac output or oxygen consumption may be more relevant or meaningful. Other potentially suitable end-points include survival and length of stay in hospital – depending upon the population studied these might require larger numbers of patients, or the use of a composite end point. Designing the details of a trial is outside the scope of this current review: it is conceivable that the induction agent will influence only one or some (or none) of any chosen number of end-points. Indeed, even a negative outcome from any trial will itself help more precisely define the role of anaesthetic induction in the wider surgical process.

Concluding remarks

We conclude that there is appropriate theoretical justification, evidence from experience (including from the authority of a number of organizations involved in healthcare), and some initial favourable clinical experimental data to support the use of ketamine in RSI of haemodynamically compromised patients. This includes patients with brain injury. Although this does not amount to definitive evidence that ketamine is superior in this scenario (which is incidentally also currently unavailable for any other agents used in RSI), at the very least the evidence justifies more widespread adoption of the drug, so that greater experience of its use may be obtained. This will help create a familiarity that will itself inform and encourage a formal trial that is needed in this field.

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