CNS Neuroscience & Therapeutics

REVIEW

CNS Neuroscience & Therapeutics

Ketamine: Use in Anesthesia

Susan Marland,[1,9] John Ellerton,[2] Gary Andolfatto,[3,4] Giacomo Strapazzon,[5] Oyvind Thomassen,[6] Brigitta Brandner,[7] Andrew Weatherall[1] & Peter Paal[8,10]

1 Care Flight, Sydney, NSW, Australia
2 Medical Officer Mountain Rescue (England and Wales), Penrith Health Centre, Penrith, UK
3 Department of Emergency Medicine, University of British Columbia, Vancouver, BC, Canada
4 The Lions Gate Hospital, North Vancouver, BC, Canada
5 EURAC Institute of Mountain Emergency Medicine, Bozen, Italy
6 Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway
7 Anaesthetics Department, University College London Hospital, London, UK
8 Department of Anesthesiology and Critical Care Medicine, Innsbruck Medical University, Innsbruck, Austria
9 Present address: Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK
10 Member of the International Commission for Alpine Emergency Medicine (ICAR Medcom)

Keywords
Analgesia; Anesthesia; Behavioral Neurology; Emergency Medical Services; Ketamine; Neuropsychopharmacology.

Correspondence
Peter Paal, DESA, EDIC, Department of Anesthesiology and Critical Care Medicine, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria.
Tel.: +43-512-504-80448;
Fax: +43-512-504-6780448;
E-mail: peter.paal@uki.at
Received 7 November 2012; revision 7 January 2013; accepted 7 January 2013.

doi: 10.1111/cns.12072

SUMMARY

The role of ketamine anesthesia in the prehospital, emergency department and operating theater settings is not well defined. A nonsystematic review of ketamine was performed by authors from Australia, Europe, and North America. Results were discussed among authors and the final manuscript accepted. Ketamine is a useful agent for induction of anesthesia, procedural sedation, and analgesia. Its properties are appealing in many awkward clinical scenarios. Practitioners need to be cognizant of its side effects and limitations.

Introduction

In the last decade, ketamine has gained popularity in the prehospital, emergency department (ED) and operating theater setting; however, its role is not well defined. Ketamine is a potent dissociative analgesic and anesthetic. Proponents advocate that its properties are appealing in many awkward clinical scenarios. In this nonsystematic review, we present useful concepts based on the available literature and our clinical experience gathered in America, Australia, and Europe.

Racemic and S-(+)-Ketamine: Differences in Effects and Dosing

Ketamine contains an asymmetrical carbon atom; this leads to two optical isomers: the S-(+) and the R-(-)isomer, which have different pharmacologic profiles [1]. The S-(+)-isomer is two-fold more effective and longer acting than the racemic mixture of both isomers; hence, half of the dosage is required with S-(+) as compared with the racemic ketamine [2–4]. S-(+)-ketamine is available only in some countries, for example, in the European Union [5], thus if not mentioned otherwise, ketamine in this text refers to the racemic ketamine and intravenous (IV) administration.

Racemic ketamine is available in three different concentrations: 10, 50, and 100 mg/mL. The 50 mg/mL solution is commonly stocked because it can be easily injected IV and intramuscular (IM). The S-(+)-ketamine solution is preservative free, which may decrease neurotoxicity. S-(+)-ketamine is available in two formulations: 5 and 25 mg/mL [6]. The incidence of side effects is comparable at equal plasma concentrations [6], although some report fewer side effects and a shorter recovery with S-(+)-ketamine.

Administration Routes

Ketamine is suitable for administration via multiple routes (Table 1), emphasizing its adaptability to many clinical scenarios [6]. The optimal route of administration of ketamine is IV, but this may not always be achievable, for example in emergencies; children; and obese patients [7].

Improved tools for intraosseous (IO) access have made this route of administration safe [8,9]. The onset of anesthesia is slightly later with IO as compared with IV injection (71 vs. 56 second) [10].

The IM route has been used for decades [11]. It is safe and predictable although painful to give [12–14]. Compared to IV, the IM route is associated with longer recovery times and a higher rate of vomiting [15]. Coadministered ondansetron reduces the incidence of emesis in children (number needed to treat [NNT] = 9) [16]. A similar antiemetic effect is seen with the concomitant use of propofol [17].

Oral racemic ketamine tastes bitter [6]. Recently, the first report of a lozenge containing ketamine 25 mg was published. The peak effect was delayed (15–30 min vs. 1–5 min IV), and the clinical response may be unpredictable.

Intranasal administration (IN) is facilitated by the large surface, uniform temperature, high permeability, and extensive vascularization of the nasal mucosa. This results in a rapid systemic absorption. These properties combined with the ease of access make this route appealing [18]. A high inter-individual peak-plasma concentration, likely to be due to swallowing and drug draining out of the nose, results in a variable effect [19,20]. On rectal administration, peak-serum concentrations are reached after 40 min [21–23].

Prehospital Applications of Ketamine

An ideal anesthetic agent for prehospital care would induce anesthesia rapidly and predictably while maintaining homeostasis (cardiovascular stability, maintenance of respiratory reflexes) [24]. In addition, a wide therapeutic range, potent analgesic effects at sub-anesthetic doses, and stable physicochemical properties in a variety of environmental conditions make the drug very attractive for prehospital analgesia. Ketamine, with its unique properties, versatility and perceived safety margin, makes it an appealing therapeutic option for prehospital and in hospital practitioners [25]. However, its uniqueness also induces clinical and logistical considerations that must be considered separately from its use in the hospital context.

Table 1 Route of administration, bioavailability, and the starting dose of ketamine

Route of administration	Bioavailability	Starting dose
Intravenous	100%	0.25–1 mg/kg (adults)* 0.25–2 mg/kg (children)* 1–2 mg/kg†
Intraosseous	100% [141,142]	0.5–1 mg/kg* 1–2 mg/kg†
Intramuscular	93% [143]	4–5 mg/kg* [144] 8–10 mg/kg† [144]
Oral	16–20% [145,146]	Children: 3–15 mg/kg* [6,145] Adults: 500 mg max.* [6]
Nasal	45–50 % [143,147]	0.25–4 mg/kg * [19,20,57] 3–9 mg/kg† [19,20,57]
Rectal	25–30% [147]	50 mg* 8–15 mg/kg† [22,23,143,147]

Note that ketamine should be titrated to the required clinical effect. *Analgesic and sedation dose. †Anesthetic dose.

Prehospital Anesthesia Induction

Prehospital intubation is undertaken in a less controlled environment than in hospital. The overall success of rapid sequence induction (RSI) is dependent on the appropriate selection of induction and neuromuscular blocking agents to provide optimal intubation conditions [24,26]. In addition, the safety and the process of anesthesia cannot be disrupted by the prehospital conditions [27,28].

An induction dose of ketamine 1–2 mg/kg IV induces dissociative anesthesia 1–2 min after IV injection. This is longer than the arm-brain circulation time desired for "rapid" unconsciousness. In a critically ill patient, ketamine provides cardiovascular stability, because it exerts sympathomimetic action in patients with an intact autonomic nervous system, which compensates for its direct negative inotropic effect on an isolated heart [29]. Additionally, as respiration is maintained through the induction phase until the onset of neuromuscular paralysis, oxygenation may be more effectively maintained [30].

Patients in shock who require ongoing resuscitation have maximal sympathetic activity [24,26]. An induction dose reduction to 0.5–1 mg/kg may be advisable as hypotension has been described in this situation [31]. The only comparable drug in terms of hemodynamic stability is etomidate. However, adrenal function may be suppressed for >24 h even after a single administration with an associated increase in mortality in septic patients. This has reduced the appeal of etomidate and its use may be declining in some centers [32–37]. Ketofol (a mixture of ketamine and propofol) has been suggested as an alternative agent with a favorable hemodynamic profile in the hospital setting [38]. It is unclear whether it offers particular advantages to ketamine in the prehospital setting.

Ketamine is appropriate for patients with traumatic brain injury (TBI), despite initial concerns about raised intracranial pressure (ICP) due to a possible increase in cerebrospinal fluid production and rise in partial arterial carbon dioxide pressure ($paCO_2$) [25,27,31,40]. As controlled ventilation, which is facilitated by anesthesia, is critical for control of $paCO_2$ to prevent secondary brain injury, this issue is not clinically relevant. Cerebral autoregulation may also be impaired in TBI with the result that cerebral perfusion pressure is critically dependent on mean arterial pressure. Hence, systemic hemodynamic stability becomes particularly vital [31]. In addition, ketamine's action via NMDA receptor antagonism has been suggested to be beneficial in TBI [25,41].

PreHospital Analgesia

The relief of pain is an essential component of prehospital care [42]. Ideal prehospital analgesia should result in the patient

experiencing pain that is no worse than mild, be able to be provided rapidly ($\leq$10 min) while maintaining responsiveness to verbal stimuli and avoiding major adverse events such as respiratory impairment, hemodynamic compromise, and excessive sedation [43]. Maintaining responsiveness to verbal stimulus is particularly valuable in the prehospital setting, where access to the patient may be compromised, and repeated assessment of level of consciousness may form a vital ongoing part of patient assessment and monitoring.

Prehospital analgesia is frequently suboptimal [44], perhaps due to concerns of adverse effects. Ketamine is a useful prehospital analgesic due to its ability to provide excellent analgesia similar to morphine or fentanyl, but with a lower incidence of respiratory depression, as demonstrated in fracture management [45], burns analgesia [46], and traumatic amputation [47]. Sedation and analgesia can usually be achieved with 0.25–1 mg/kg (Table 1). Ketamine may be particularly useful in a patient in whom parenteral opioids have already been administered without adequate pain relief. For example, coadministered ketamine (average 40 mg IV) and morphine (5 mg IV) are superior to morphine (mean 14 mg IV) alone in the prehospital setting [48]. This is best achieved gradually by giving incremental doses while maintaining verbal contact.

Prehospital Procedural Sedation

Ketamine has an established role in procedural sedation in the ED, including pediatrics. Its use in disaster and limited resource situations is well recorded. Particular scenarios may arise where surgical procedures are required in the prehospital context. These include acute life-threatening situations such as managing major hemorrhage, and amputation to facilitate patient extrication. In a retrospective review, 32 patients received ketamine during the insertion of a chest drain; no relevant complications occurred [12]. When compared to alternative sedatives, the analgesia provided by ketamine is particularly valuable. Descriptions of the use of benzodiazepines alone reveal cases where administration of such an agent leaves the patient aware of the procedure without analgesia [49]. In the context of prehospital procedural sedation, it remains important to administer supplemental oxygen and provide as much patient monitoring as is practical.

Special Circumstances

The Combative Patient

The combative, agitated patient requiring RSI, and tracheal intubation presents a difficult clinical scenario [50]. These patients often prevent or obstruct meaningful clinical intervention, contributing to deterioration in their clinical state. While it is essential to identify and treat any factors contributing to their agitation, gaining control of the clinical situation prior to undertaking a formal RSI is necessary. Embarking on a RSI without optimizing patient position, ensuring pre-oxygenation and good IV access makes complications much more likely [26]. When dealing with a combative trauma patient, the clinician is left with a few alternatives, for example, physical restraint or sedation with benzodiazepines, antipsychotic drugs or ketamine [51,52]. Ketamine can be administered IM if IV access is not possible. This enables optimization of the patient before RSI. Using a single drug (e.g., IV ketamine 1–2 mg/kg; IM 8–10 mg/kg [5,6]) for this purpose simplifies the process, saving time, and decreasing drug errors.

Patient Extrication

Ketamine is a particularly useful analgesic and sedative in the trapped patient, to whom there may be limited access. The extrication may take hours; repeated bolus doses of ketamine can allow excellent analgesia and painless extraction [52]. Alternatively, extrication may need to be expedited for a variety of reasons, and provision of analgesia may facilitate more rapid release of the patient.

Pediatric Patients

Control of pain and stress in children who enter into the emergency medical system is a vital component of emergency care [53]. A number of barriers exist to achieving adequate pediatric analgesia; these include unwanted attention from authority figures; perceived superiority of hospital care; difficulty obtaining IV access, and a culture of low-dose administration [54]. All played important roles in an overall preference to defer pediatric analgesia [55]. Ketamine is suitable for use in pediatrics for analgesia, procedural sedation, and anesthesia. In a review of its use in 164 children seen by the London Helicopter Medical Service, ketamine was predominantly used in awake nontrapped patients with blunt trauma for procedural sedation and analgesia; no major side effects were reported [56]. The ability to administer ketamine by a number of routes also makes it a valuable tool in pediatric care. For example, IN ketamine in pediatric burns is recommended at a dose of 0.25–0.5 mg/kg (Table 1) [57].

Disaster Medicine

Disaster medicine represents an area where the ideal qualities of ketamine as a prehospital agent are at the fore, and it has therefore been widely used as a field anesthetic in austere conditions. Experience from Banda Aceh [58], Kashmir [59], and Haiti [60] demonstrates its usefulness. Where possible, it is appealing to supplement ketamine anesthesia with regional anesthesia where there is a paucity of equipment.

In Kashmir, 149 patients received emergency surgery using ketamine anesthesia with benzodiazepine premedication. This was safe, effective, and had a low incidence of major adverse effects [59]. In Haiti, where there were many cases, sedation was frequently employed using IV midazolam (0.05–0.1 mg/kg) and ketamine (1–2 mg/kg) with augmentation with local anesthesia where possible [60]. This technique allowed the patient to remain spontaneously breathing, and reduced recovery time and staffing requirements.

Limitations

Ketamine has a number of side effects, which can be managed adequately in the prehospital setting if anticipated and identified. For instance, emergence phenomena with ketamine have pre-

vented its widespread use in hospital practice for general anesthesia. While emergence phenomena will rarely be of significance for the prehospital practitioner, the hospital team may have to manage such reactions later during the patient's hospital care. One of ketamine's positive features is that it has minimal effect on central respiratory drive if given slowly, although rapid IV injection can cause transient apnea [6]. Ketamine increases salivary secretions, which may increase the incidence of laryngospasm. Many of these reported effects may be due to partial airway obstruction, which usually responds to simple airway maneuvers [6]. Secretions can be anticipated and some recommend to manage them with a small dose of an antisialogogue, for example atropine (0.01 mg/kg) [61].

Hypothermia is a common comorbidity during the prehospital phase. The interplay between ketamine and hypothermia is poorly researched. Ketamine is good at minimizing the fall in core temperature usually associated with anesthesia as it reduces the magnitude of redistribution hypothermia [62]. However, the sympathomimetic effects on an irritable hypothermic heart and its reduced metabolism have potential for serious side effects that have not been researched.

Ketamine Use in the Emergency Department

Intravenous ketamine has long been a mainstay for pediatric procedural sedation in the ED [63]. More recently, there has been increasing interest in the use of ketamine for adult procedural sedation, often combined with sedatives such as propofol or midazolam [64–66].

The characteristic dissociative state seen with ketamine becomes apparent with doses of 1.0–1.5 mg/kg and is characterized by a trance-like cataleptic state in which there is potent analgesia, sedation, and amnesia. Spontaneous respirations, airway reflexes, and cardiovascular stability are maintained [67]. Absolute contraindications to IV ketamine sedation are age <3 months and schizophrenia. Relative contraindications include increased ICP, glaucoma or acute globe injury. Caution is suggested in patients with cardiovascular disease, porphyria or thyroid disorder [15].

For ED procedural sedation, a loading dose (1.5–2.0 mg/kg IV in children or 1.0 mg/kg IV in adults) administered in 30–60 second is recommended (Table 1). For shorter procedures, a single loading dose is adequate, while for longer procedures, the dissociative state can be maintained with incremental doses of 0.5–1 mg/kg [15].

Common adverse events associated with ketamine sedation include recovery agitation (1–2% in children, 10–20% in adults), muscular hypertonicity, and emesis (5–15%). Other potential adverse events such as laryngospasm and hypersalivation are rare [15,68]. Pretreatment with atropine or glycopyrrolate is no longer routinely recommended [15].

The use of ketamine and propofol mixed in a single syringe (so-called "ketofol") has become a popular agent for ED procedural sedation as the opposing physiological effects of ketamine and propofol can be used to clinical advantage as ketamine mitigates propofol-induced hypotension, and propofol mitigates ketamine-induced vomiting and recovery agitation [69]. The drugs are chemically compatible when mixed [70] and appear to have a synergistic effect as deep sedation is reliably achieved with half the dosage requirements of each drug alone (average 0.7 mg/kg of each drug) [71]. Two randomized controlled trials have shown improved sedation consistency with ketofol compared with propofol alone, and no difference in the incidence of adverse respiratory events [71,72]. Administering the agents in separate syringes is also commonly used for procedural sedation. In this circumstance, subdissociative ketamine is administered as an analgesic agent, with subsequent titration of sedation depth with intermittent propofol boluses of 10–40 mg every 2–3 min [73–75]. Ketamine also reduces morphine requirements in ED trauma patients [76].

Ketamine in the Operating Theater

Neurotoxicity

Ketamine provides profound analgesia after neuraxial application, which has triggered great interest in its potential benefits during neuraxial anesthesia. However, the widespread use of ketamine has been hampered due to fear of potential neurotoxicity. Animal studies showed neurotoxic effects for many local anesthetics [77], but not for ketamine in doses commonly used for regional anesthesia [78,79]. Compared with other spinal agents, for example, local anesthetics and opioids, ketamine has no life-threatening cardiovascular, neurological or respiratory side effects if administered unintentionally IV or intrathecally [78,80]. However, in human neuroblastoma cells and rat astrocytes, the combined toxicity of ketamine and lidocaine was additive [81]. In one animal study, high intrathecal ketamine (1.6 mg/kg) resulted in three dead animals of 30 [82]. Neurotoxicity was reported in a patient after long-term intrathecal administration of ketamine with preservatives due to chronic pain [83]. Preservatives may be causative of this neurotoxicity, but this is unproven. In neonatal rats, ketamine, which is a potent inductor of neural apoptosis, has a therapeutic index (i.e., toxic dose/analgesic dose) <1 [79], while the same index is >300 for morphine and clonidine [84]. Thus, a recent editorial cautioned against using ketamine in neonatal caudal blocks [85].

Ketamine in Children

Regional Anesthesia

The efficiency of caudal ketamine has been reported by several studies (Tables S1 and S2). With inguinal herniotomy, ketamine 0.5 mg/kg added to bupivacaine 0.25% as compared with plain bupivacaine 0.25% was more analgesic [86]. Also, ketamine 0.5 mg/kg as compared with clonidine 2 μg/kg or epinephrine 5 μg/kg added to bupivacaine 0.25% provided longer analgesia after orchidopexy (12.5 vs. 5.8 vs. 3.2 h) [87]. Increasing dosages of ketamine (0.25, 0.5, and 1 mg/kg) prolonged analgesia after orchidopexy (7.9 vs. 11 vs. 16.6 h) [88]. There was no difference between the groups regarding motor block, sedation, and urinary retention but slight psychogenic side effects were noted with ketamine 1 mg/kg. Thus, the most appropriate dose is likely to be 0.5 mg/kg [88]. In children undergoing orchidopexy, ketamine was added either to bupivacaine 0.125% or 0.25%; analgesia was

equivalent but motor-block regression faster with bupivacaine 0.125% (8 vs. 9.5 h) [89]. Ropivacaine 0.2% and ketamine 0.25 mg/kg provided analgesia for 12 h as compared with 3 h for plain ropivacaine 0.2% [90]. During spinal anesthesia, an IV propofol 3.2 mg/kg/h per ketamine 0.8 mg/kg/h infusion conveyed better sedation than propofol 4 mg/kg/h alone (n = 40) [91].

Caudal anesthesia with S-(+)-ketamine 0.5 and 1 mg/kg was comparable to bupivacaine 0.25% with epinephrine 1:200,000 (300 ± 96 min vs. 273 ± 123 min vs. 203 ± 117 min) [92]. After inguinal hernia repair, S-(+)-ketamine produced 8.8 h analgesia, as compared with 1.8 h with IM ketamine [93]. After subumbilical surgery, the addition of S-(+)-ketamine 0.5 mg/kg as compared with clonidine 2 μg/kg to ropivacaine 0.2% or plain ropivacaine had a longer analgesic effect (11.7 vs. 8.2 vs. 4.8 h) [94]. Similarly, after such surgery, S-(+)-ketamine 0.5 mg/kg with ropivacaine 0.1% prolonged analgesia compared to plain ropivacaine [94]. S-(+)-ketamine 1 mg/kg plus clonidine 1 μg/kg also prolonged analgesia as compared with S-(+)-ketamine 1 mg/kg alone [95].

A recent quantitative systematic review of randomized controlled trials on adding ketamine to pediatric caudal anesthesia concluded that ketamine prolonged analgesia compared with a local anesthetic alone (mean difference 5.6 h) with few side effects, although uncertainties over neurotoxicity still need to be clarified [96]. Another meta-analysis stated that caudal ketamine in pediatrics was associated with decreased postoperative pain and nonopioid analgesic requirement. However, ketamine failed to exhibit an opioid-sparing effect [97].

General Anesthesia

After tonsillectomy (n = 60), ketamine 0.5 mg/kg added to fentanyl 1 mg/kg improved analgesia without delaying hospital discharge [98]. Also, ketamine 0.5 mg/kg added to anesthesia induction with sevoflurane 5% and alfentanil 10 μg/kg (n = 50) improved intubation conditions in spontaneously breathing children while preserving hemodynamic stability [99]. Similarly, in children with congenital heart disease (n = 50), hemodynamics were better preserved and adverse respiratory effects were fewer and milder after anesthesia induction with IM ketamine 5 mg/kg as compared with sevoflurane 3% [100]. Hemodynamics were also better preserved in oncology children (n = 47) undergoing procedural anesthesia with ketamine 0.5 mg/kg and propofol 0.5 mg/kg as compared with propofol 1 mg/kg [101]. Successful anesthesia was reported for MRI with a multidrug approach consisting of midazolam, ketamine, and propofol [102].

Ketamine 0.25 mg/kg but not propofol 1 mg/kg attenuated sevoflurane-induced postoperative agitation (n = 60) [103]. Less agitation as compared to saline was also reported by two other studies [104,105].

Ketamine in Adults

Regional Anesthesia

After cesarean section (n = 188), 10 mg IV ketamine supplementing spinal bupivacaine, fentanyl, and morphine, and IV ketorolac had no additional postoperative analgesic benefit [106], while S-(+)-ketamine 0.05 mg/kg compared with fentanyl 25 μg added to 10 mg bupivacaine 0.5% enhanced the segmental spread and shortened the duration of analgesia [107]. In women undergoing spinal anesthesia during brachytherapy for cervix carcinoma (n = 60) with either bupivacaine 10 mg or bupivacaine, 7.5 mg plus ketamine 25 mg analgesia was comparable but duration of motor block and requirement of fluids were less in the ketamine group. However, more patients complained of psychomimetic effects and nausea and vomiting in this group [108]. When comparing spinal anesthesia for transurethral prostatectomy (n = 40) with bupivacaine 10 mg or bupivacaine 7.5 mg plus S-(+)-ketamine 0.1 mg/kg onset of motor and sensory block were shorter in the bupivacaine plus S-(+)-ketamine group [109]. In patients (n = 40) assigned to a sedation of propofol (1.5 mg/kg/h) vs. propofol-ketamine (1.2 mg/kg/h and 0.3 mg/kg/h) during spinal anesthesia, the latter conveyed more hemodynamic stability [110]. Ketamine sedation 0.5 mg/kg/h during spinal anesthesia for arthroscopic knee surgery attenuated ischemia-reperfusion markers (n = 30) [111]. Remifentanil-induced postoperative hyperalgesia may be prevented by ketamine 0.5 mg/kg at incision followed by 5 μg/kg/h until skin closure and 2 μg/kg/h for 48 h [112].

General Anesthesia

S-(+)-ketamine (1–3 mg/kg bolus, followed by 2–4 mg/kg/h) during elective coronary-artery-bypass graft (CABG) surgery exerts antiinflammatory effects during and after cardiopulmonary bypass (n = 128) [113]. Hemodynamics are also improved and antiinflammatory effects were evident in cardiac surgery patients (n = 50) with ketamine 0.25 and 0.5 mg/kg as compared to placebo [114]. No antiinflammatory effects were seen after single-dose administration of ketamine 0.5 mg/kg after CABG-off-pump surgery (n = 50) [115]. A systematic review concluded that intraoperative ketamine exerts antiinflammatory effects [116]. In hemodynamically stable elective CABG-patients (n = 209), S-(+)-ketamine did not accentuate postoperative troponin-T rises, and hemodynamic function was comparable [117]. Propofol co-induction with 0.5 mg/kg ketamine compared with propofol alone may be propofol sparing, resulting in less hemodynamic depression; this may be advantageous in hemodynamically unstable or fragile patients [118,119].

Propofol (1.5 mg/kg) plus ketamine (0.8 mg/kg) provided better anesthesia in patients with depressive disorders undergoing electroconvulsive therapy [120]. No postoperative beneficial analgesia was conveyed after cesarian section (n = 140) when ketamine 0.25–1 mg/kg was added during anesthesia induction [121]. Similarly, anesthesia with propofol/ketamine vs. propofol/alfentanil for dilatation and curretage (n = 60) was comparable but the ketamine group required more time before orientation returned [122]. After thoracotomy (n = 49), ketamine 0.05 mg/kg/h, as compared to saline, added to epidural ropivacaine and morpine provided better analgesia [123]. Similarly, epidural as compared with IM ketamine (1 mg/kg in both groups, n = 60) reduced intra- and postoperative analgesia requirement [124].

After cholecystectomy (n = 120), ketamine 2 mg/kg subcutaneously infiltrated vs. 1 mg/kg IV 15 min before surgery provided better analgesia for 24 h [125]. Ketamine 0.5 mg/kg on induction

followed by 10 μg/kg/h until wound closure decreases perioperative opiate requirements in opiate-dependent patients with chronic back pain undergoing back surgery (n = 102) [126]. Perioperative ketamine 0.15 mg/kg, as compared with saline, reduced pain in women undergoing laparascopic surgery (n = 135) [127].

Psychogenic Effects

Ketamine has been recognized as a potent psychedelic drug and dissociative anesthetic since its introduction into clinical practice. It provokes imaginative, dissociative states, and psychotic symptoms up to schizophrenia due to its NMDA-antagonistic action [128–130] as well as severely impairing semantic and episodic memory when used in sub-anesthetic doses [130]. A dissociative effect of *loss-of-self*, inability to move the body, and isolation of mind from body is reported when ketamine is used as a sedative or analgesic. These are acute effects; little is known of the longer-term sequelae [131]. Used as an anesthetic, ketamine can cause emergence phenomena. These have been variously described as a floating sensation, vivid pleasant dreams, nightmares, hallucinations, and delirium. The phenomena are more common in >16 year, in females, in shorter operative procedures, and those receiving large doses particularly when these are administered quickly [40,63]. Intravenous ketamine in healthy volunteers (n = 40) without premedication resulted in more mental abnormalities than thiopentone, these changes were not present by the following day [132]. Benzodiazepines effectively prevent these phenomena. Midazolam is particularly favoured and has been shown to reduce the incidence of unpleasant dreams when compared with diazepam (NNT = 6) [65,133]. Propofol and various other benzodiazepines such as lorazepam, diazepam, flunitrazepam are effective but the latter can delay recovery [134]. Benzodiazepines are not coadministered regularly with ketamine. For example, in a case series, midazolam was coadministered only to 12 of 32 patients (38%) [42,135]. A recent trial (n = 100) reported that a positive persuasion may reduce unpleasant sensations [136].

In children, mild emergence reactions can happen up to 15 days after ketamine [137]. Dose is important. For example, no more nightmares than in controls were described in children (n = 90) after 0.5 mg/kg ketamine [138] but after a dose of 7 mg/kg 7.1% described them. In 301 children given ketamine 0.5–2.5 mg/kg with midazolam, the incidence of bad dreams was ~1.7% after the first postoperative night [139]. In adults, no psychological effects have been reported with subanesthetic doses (0.1 mg/kg); however, at 0.5 mg/kg, some anxiety and paranoia have been reported [129]. Unpleasant dreams seem to be due to the diminishing positive effect of positive emotions rather than intensification of negative emotions [140]. Despite these sequelae, ketamine is regaining popularity as a sedative, analgesic, and anesthetic agent.

Conclusions

Ketamine is a useful agent for induction of anesthesia, procedural sedation, and analgesia. Its properties are appealing in many awkward clinical scenarios. Practitioners need to be cognizant of its side effects and limitations.

Acknowledgments

Susan Marland and Andrew Weatherall compiled the prehospital section of this article, John Ellerton and Peter Paal supervised this study and wrote the anesthesia in children and adults part, Gary Andolfatto wrote the ED part, Giacomo Strapazzon and Oyvind Thomassen compiled the part on different application routes and the difference between Ketamine racemat and (S) and Brigitta Brandner wrote the part on psychogenic effects. All authors listed on the title page have made substantial contributions, read and discussed the manuscript and agree to its submission in the present form to CNS Neuroscience & Therapeutics.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Ryder S, Way WL, Trevor AJ. Comparative pharmacology of the optical isomers of ketamine in mice. *Eur J Pharmacol* 1978;**49**:15–23.
2. Loh G, Dalen D. Low-dose ketamine in addition to propofol for procedural sedation and analgesia in the emergency department. *Ann Pharmacother* 2007;**41**:485–492.
3. Benthuysen JL, Hance AJ, Quam DD, et al. Comparison of isomers of ketamine on catalepsy in the rat and electrical activity of the brain and behavior in the cat. *Neuropharmacology* 1989;**28**:1003–1009.
4. Meller ST. Ketamine: Relief from chronic pain through actions at the NMDA receptor? *Pain* 1996;**68**:435–436.
5. Ellerton J, Paal P, Brugger H. Prehospital use of ketamine in mountain rescue. *Emerg Med J* 2009;**26**:760–761.
6. Craven R. Ketamine. *Anaesthesia* 2007;**62**(Suppl 1):48–53.
7. Brown D, Brugger H, Boyd J, et al. Accidental hypothermia. *N Engl J Meg* 2012;**367**:1930–1938.
8. Olaussen A, Williams B. Intraosseous access in the prehospital setting: Literature review. *Prehosp Disaster Med* 2012;**27**:468–472.
9. Helm M, Hossfeld B, Schlechtriemen T, et al. Use of intraosseous infusion in the German air rescue service: Nationwide analysis in the time period 2005 to 2009. *Anaesthesist* 2011;**60**:1119–1125.
10. Aliman AC, Piccioni Mde A, Piccioni JL, et al. Intraosseous anesthesia in hemodynamic studies in children with cardiopathy. *Rev Bras Anestesiol* 2011;**61**:41–49.
11. Walker AK. Intramuscular ketamine in a developing country. Experience in the British Solomon Islands. *Anaesthesia* 1972;**27**:408–414.
12. Bredmose PP, Lockey DJ, Grier G, et al. Pre-hospital use of ketamine for analgesia and procedural sedation. *Emerg Med J* 2009;**26**:62–64.
13. Green SM, Rothrock SG, Harris T, et al. Intravenous ketamine for pediatric sedation in the emergency department: Safety profile with 156 cases. *Acad Emerg Med* 1998;**5**:971–976.
14. Green SM, Rothrock SG, Lynch EL, et al. Intramuscular ketamine for pediatric sedation in the emergency department: Safety profile in 1,022 cases. *Ann Emerg Med* 1998;**31**:688–697.
15. Green SM, Roback MG, Kennedy RM, et al. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med* 2011;**57**:449–461.
16. Langston WT, Wathen JE, Roback MG, et al. Effect of ondansetron on the incidence of vomiting associated with ketamine sedation in children: A double-blind, randomized, placebo-controlled trial. *Ann Emerg Med* 2008;**52**:30–34.
17. Shah A, Mosdossy G, McLeod S, et al. A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. *Ann Emerg Med* 2011;**57**:425–433 e2.
18. Brockmeyer DM, Kendig JJ. Selective effects of ketamine on amino acid-mediated pathways in neonatal rat spinal cord. *Br J Anaesth* 1995;**74**:79–84.
19. Weber F, Wulf H, Gruber M, et al. S-ketamine and s-norketamine plasma concentrations after nasal and i.v. administration in anesthetized children. *Paediatr Anaesth* 2004;**14**:983–988.
20. Huge V, Lauchart M, Magerl W, et al. Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. *Eur J Pain* 2010;**14**:387–394.
21. Malinovsky JM, Lejus C, Servin F, et al. Plasma concentrations of midazolam after i.v., nasal or rectal administration in children. *Br J Anaesth* 1993;**70**:617–620.

22. Idvall J, Holasek J, Stenberg P. Rectal ketamine for induction of anaesthesia in children. *Anaesthesia* 1983;**38**:60–64.
23. Malaquin JM. Ketamine via rectal route for the induction of pediatric anesthesia. *Cah Anesthesiol* 1984;**32**:373–374.
24. Morris C, Perris A, Klein J, et al. Anaesthesia in haemodynamically compromised emergency patients: Does ketamine represent the best choice of induction agent? *Anaesthesia* 2009;**64**:532–539.
25. Sehdev RS, Symmons DA, Kindl K. Ketamine for rapid sequence induction in patients with head injury in the emergency department. *Emerg Med Australas* 2006;**18**:37–44.
26. Braun P, Wenzel V, Paal P. Anesthesia in prehospital emergencies and in the emergency department. *Curr Opin Anaesthesiol* 2010;**23**:500–506.
27. Paal P, Herff H, Mitterlechner T, et al. Anaesthesia in prehospital emergencies and in the emergency room. *Resuscitation* 2010;**81**:148–154.
28. Bernard SA. Paramedic intubation of patients with severe head injury: A review of current Australian practice and recommendations for change. *Emerg Med Australas* 2006;**18**:221–228.
29. Stowe DF, Bosnjak ZJ, Kampine JP. Comparison of etomidate, ketamine, midazolam, propofol, and thiopental on function and metabolism of isolated 7 hearts. *Anesth Analg* 1992;**74**:547–558.
30. Filanovsky Y, Miller P, Kao J. Myth: Ketamine should not be used as an induction agent for intubation in patients with head injury. *CJEM* 2010;**12**:154–157.
31. Braun P, Paal P. Beware of etomidate and cricoid pressure during rapid sequence induction. *Intensive Care Med* 2010;**36**:2160.
32. Morris C, McAllister C. Etomidate for emergency anaesthesia; mad, bad and dangerous to know? *Anaesthesia* 2005;**60**:737–740.
33. Hildreth AN, Mejia VA, Maxwell RA, et al. Adrenal suppression following a single dose of etomidate for rapid sequence induction: A prospective randomized study. *J Trauma* 2008;**65**:573–579.
34. Chan CM, Mitchell AL, Shorr AF. Etomidate is associated with mortality and adrenal insufficiency in sepsis: A meta-analysis. *Crit Care Med* 2012;**40**:2945–2953.
35. Jabre P, Combes X, Lapostolle F, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: A multicentre randomised controlled trial. *Lancet* 2009;**374**:293–300.
36. den Brinker M, Hokken-Koelega AC, Hazelzet JA, et al. One single dose of etomidate negatively influences adrenocortical performance for at least 24 h in children with meningococcal sepsis. *Intensive Care Med* 2008;**34**:163–168.
37. Smischney NJ, Beach ML, Loftus RW, et al. Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: A randomized, controlled trial. *J Trauma Acute Care Surg* 2012;**73**:94–101.
38. Green SM, Sherwin TS. Incidence and severity of recovery agitation after ketamine sedation in young adults. *Am J Emerg Med* 2005;**23**:142–144.
39. Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency 8 department. *Ann Emerg Med* 2007;**49**:23–30.
40. Mort TC. Preoxygenation in critically ill patients requiring emergency tracheal intubation. *Crit Care Med* 2005;**33**:2672–2675.
41. Giza CC, Maria NS, Hovda DA. N-methyl-D-aspartate receptor subunit changes after traumatic injury to the developing brain. *J Neurotrauma* 2006;**23**:950–961.
42. Porter K. Ketamine in prehospital care. *Emerg Med J* 2004;**21**:351–354.
43. Park CL, Roberts DE, Aldington DJ, et al. Prehospital analgesia: Systematic review of evidence. *J R Army Med Corps* 2010;**156**(4 Suppl 1):295–300.
44. McManus JG Jr, Sallee DR Jr. Pain management in the prehospital environment. *Emerg Med Clin North Am* 2005;**23**:415–431.
45. Kennedy RM, Porter FL, Miller JP, et al. Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies. *Pediatrics* 1998;**102**:956–963.
46. McGuinness SK, Wasiak J, Cleland H, et al. A systematic review of ketamine as an analgesic agent in adult burn injuries. *Pain Med* 2011;**12**:1551–1558.
47. Bonanno FG. Ketamine in war/tropical surgery (a final tribute to the racemic mixture). *Injury* 2002;**33**:323–327.
48. Jennings PA, Cameron P, Bernard S, et al. Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: A randomized controlled trial. *Ann Emerg Med* 2012;**59**:497–503.
49. Maningas PA, Robison M, Mallonee S. The EMS response to the Oklahoma City bombing. *Prehosp Disaster Med* 1997;**12**:80–85.
50. AAGBI. Pre-Hospital Anaesthesia. Safety Guideline. 2009. Available from: http://www.aagbi.org/sites/default/files/prehospital_glossy09.pdf [Accessed 6 September, 2012].
51. Melamed E, Oron Y, Ben-Avraham R, et al. The combative multitrauma patient: A protocol for prehospital management. *Eur J Emerg Med* 2007;**14**:265–268.
52. Cottingham R, Thomson K. Use of ketamine in prolonged entrapment. *J Accid Emerg Med* 1994;**11**:189–191.
53. Zempsky WT, Cravero JP. Relief of pain and anxiety in pediatric patients in emergency medical systems. *Pediatrics* 2004;**114**:1348–1356.
54. Abdi Z. The paediatric analgesia wheel: Are you ready to roll? *Lancet* 2009;**373**:1831–1832.
55. Williams DM, Rindal KE, Cushman JT, et al. Barriers to and enablers for prehospital analgesia for pediatric patients. *Prehosp Emerg Care* 2012;**16**:519–526.
56. Bredmose PP, Grier G, Davies GE, et al. Pre-hospital use of ketamine in paediatric trauma. *Acta Anaesthesiol Scand* 2009;**53**:543–545.
57. Reid C, Hatton R, Middleton P. Case report: Prehospital use of intranasal ketamine for paediatric burn injury. *Emerg Med J* 2011;**28**:328–329.
58. Paix BR, Capps R, Neumeister G, et al. Anaesthesia in a disaster zone: A report on the experience of an Australian medical team in Banda Aceh following the 'Boxing Day Tsunami'. *Anaesth Intensive Care* 2005;**33**:629–634.
59. Mulvey JM, Qadri AA, Maqsood MA. Earthquake injuries and the use of ketamine for surgical procedures: The Kashmir experience. *Anaesth Intensive Care* 2006;**34**:489–494.
60. Rice MJ, Gwertzman A, Finley T, et al. Anesthetic practice in Haiti after the 2010 earthquake. *Anesth Analg* 2010;**111**:1445–1449.
61. Kye YC, Rhee JE, Kim K, et al. Clinical effects of adjunctive atropine during ketamine sedation in pediatric emergency patients. *Am J Emerg Med* 2012;**30**:1981–1985.
62. Ikeda T, Kazama T, Sessler DI, et al. Induction of anesthesia with ketamine reduces the magnitude of redistribution hypothermia. *Anesth Analg* 2001;**93**:934–938.
63. Green SM, Johnson NE. Ketamine sedation for pediatric procedures: Part 2. Review and implications. *Ann Emerg Med* 1990;**19**:1033–1046.
64. Newton A, Fitton L. Intravenous ketamine for adult procedural sedation in the emergency department: A prospective cohort study. *Emerg Med J* 2008;**25**:498–501.
65. Sener S, Eken C, Schultz CH, et al. Ketamine with and without midazolam for emergency department sedation in adults: A randomized controlled trial. *Ann Emerg Med* 2011;**57**:109–114 e2.
66. Arora S. Combining ketamine and propofol ("ketofol") for emergency department procedural sedation and analgesia: A review. *West J Emerg Med* 2008;**9**:20–23.
67. Green SM, Krauss B. Should I give ketamine i.v. or i.m.? *Ann Emerg Med* 2006;**48**:613–614.
68. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008;**26**:985–1028.
69. Green SM, Andolfatto G, Krauss B. Ketofol for procedural sedation? Pro and con *Ann Emerg Med* 2011;**57**:444–448.
70. Donnelly R, Willman E, Andolfatto G. Stability of ketamine-propofol mixtures for procedural sedation and analgesia in the emergency department. *Can J Hosp Pharm* 2008;**61**:426–430.
71. Andolfatto G, Abu-Laban RB, Zed PJ, et al. Ketamine-propofol combination (ketofol) versus propofol alone for emergency department procedural sedation and analgesia: A randomized double-blind trial. *Ann Emerg Med* 2012;**59**:504–512 e1-2
72. David H, Shipp J. A randomized controlled trial of ketamine/propofol versus propofol alone for emergency department procedural sedation. *Ann Emerg Med* 2011;**57**:435–441.
73. Messenger DW, Murray HE, Dungey PE, et al. Subdissociative-dose ketamine versus fentanyl for analgesia during propofol procedural sedation: A randomized clinical trial. *Acad Emerg Med* 2008;**15**:877–886.
74. Sharieff GQ, Trocinski DR, Kanegaye JT, et al. Ketamine-propofol combination sedation for fracture reduction in the pediatric emergency department. *Pediatr Emerg Care* 2007;**23**:881–884.
75. Lester L, Braude DA, Niles C, et al. Low-dose ketamine for analgesia in the ED: A retrospective case series. *Am J Emerg Med* 2010;**28**:820–827.
76. Galinski M, Dolveck F, Combes X, et al. Management of severe acute pain in emergency settings: Ketamine reduces morphine consumption. *Am J Emerg Med* 2007;**25**:385–390.
77. Radwan IA, Saito S, Goto F. The neurotoxicity of local anesthetics on growing neurons: A comparative study of lidocaine, bupivacaine, mepivacaine, and ropivacaine. *Anesth Analg* 2002;**94**:319–324.
78. Tobias JD. Caudal epidural block: A review of test dosing and recognition of systemic injection in children. *Anesth Analg* 2001;**93**:1156–1161.
79. Walker SM, Westin BD, Deumens R, et al. Effects of intrathecal ketamine in the neonatal rat: Evaluation of apoptosis and long-term functional outcome. *Anesthesiology* 2010;**113**:147–159.
80. de Beer DA, Thomas ML. Caudal additives in children–solutions or problems? *Br J Anaesth* 2003;**90**:487–498.
81. Werdehausen R, Braun S, Hermanns H, et al. The influence of adjuvants used in regional anesthesia on lidocaine-induced neurotoxicity *in vitro*. *Reg Anesth Pain Med* 2011;**36**:436–443.
82. Ahuja BR. Analgesic effect of intrathecal ketamine in rats. *Br J Anaesth* 1983;**55**:991–995.
83. Stotz M, Oehen HP, Gerber H. Histological findings after long-term infusion of intrathecal ketamine for chronic pain: A case report. *J Pain Symptom Manage* 1999;**18**:223–228.
84. Westin BD, Walker SM, Deumens R, et al. Validation of a preclinical spinal safety model: Effects of intrathecal morphine in the neonatal rat. *Anesthesiology* 2010;**113**:183–199.
85. Lonnqvist PA, Walker SM. Ketamine as an adjunct to caudal block in neonates and infants: Is it time to re-evaluate? *Br J Anaesth* 2012;**109**:138–140.

86. Naguib M, Sharif AM, Seraj M, et al. Ketamine for caudal analgesia in children: Comparison with caudal bupivacaine. *Br J Anaesth* 1991;**67**:559–564.
87. Cook B, Grubb DJ, Aldridge LA, et al. Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. *Br J Anaesth* 1995;**75**:698–701.
88. Semple D, Findlow D, Aldridge LM, et al. The optimal dose of ketamine for caudal epidural blockade in children. *Anaesthesia* 1996;**51**:1170–1172.
89. Johnston P, Findlow D, Aldridge LM, et al. The effect of ketamine on 0.25% and 0.125% bupivacaine for caudal epidural blockade in children. *Paediatr Anaesth* 1999;**9**:31–34.
90. Lee HM, Sanders GM. Caudal ropivacaine and ketamine for postoperative analgesia in children. *Anaesthesia* 2000;**55**:806–810.
91. Singh R, Batra YK, Bharti N, et al. Comparison of propofol versus propofol-ketamine combination for sedation during spinal anesthesia in children: Randomized clinical trial of efficacy and safety. *Paediatr Anaesth* 2010;**20**:439–444.
92. Marhofer P, Krenn CG, Plochl W, et al. S(+)-ketamine for caudal block in paediatric anaesthesia. *Br J Anaesth* 2000;**84**:341–345.
93. Koinig H, Marhofer P, Krenn CG, et al. Analgesic effects of caudal and intramuscular S(+)-ketamine in children. *Anesthesiology* 2000;**93**:976–980.
94. De Negri P, Ivani G, Visconti C, et al. How to prolong postoperative analgesia after caudal anaesthesia with ropivacaine in children: S-ketamine versus clonidine. *Paediatr Anaesth* 2001;**11**:679–683.
95. Hager H, Marhofer P, Sitzwohl C, et al. Caudal clonidine prolongs analgesia from caudal S(+)-ketamine in children. *Anesth Analg* 2002;**94**:1169–1172.
96. Schnabel A, Poepping DM, Kranke P, et al. Efficacy and adverse effects of ketamine as an additive for paediatric caudal anaesthesia: A quantitative systematic review of randomized controlled trials. *Br J Anaesth* 2011;**107**:601–611.
97. Dahmani S, Michelet D, Abback PS, et al. Ketamine for perioperative pain management in children: A meta-analysis of published studies. *Paediatr Anaesth* 2011;**21**:636–652.
98. Elshammaa N, Chidambaran V, Housny W, et al. Ketamine as an adjunct to fentanyl improves postoperative analgesia and hastens discharge in children following tonsillectomy – a prospective, double-blinded, randomized study. *Paediatr Anaesth* 2011;**21**:1009–1014.
99. Kim KS, Kwak HJ, Min SK, et al. The effect of ketamine on tracheal intubating conditions without neuromuscular blockade during sevoflurane induction in children. *J Anesth* 2011;**25**:195–199.
100. Sungur Ulke Z, Kartal U, Orhan Sungur M, et al. Comparison of sevoflurane and ketamine for anesthetic induction in children with congenital heart disease. *Paediatr Anaesth* 2008;**18**:715–721.
101. Aouad MT, Moussa AR, Dagher CM, et al. Addition of ketamine to propofol for initiation of procedural anesthesia in children reduces propofol consumption and preserves hemodynamic stability. *Acta Anaesthesiol Scand* 2008;**52**:561–565.
102. Shorrab AA, Demian AD, Atallah MM. Multidrug intravenous anesthesia for children undergoing MRI: A comparison with general anesthesia. *Paediatr Anaesth* 2007;**17**:1187–1193.
103. Tsai PS, Hsu YW, Lin CS, et al. Ketamine but not propofol provides additional effects on attenuating sevoflurane-induced emergence agitation in midazolam premedicated pediatric patients. *Paediatr Anaesth* 2008;**18**:1114–1115.
104. Abu-Shahwan I, Chowdary K. Ketamine is effective in decreasing the incidence of emergence agitation in children undergoing dental repair under sevoflurane general anesthesia. *Paediatr Anaesth* 2007;**17**:846–850.
105. Dalens BJ, Pinard AM, Letourneau DR, et al. Prevention of emergence agitation after sevoflurane anesthesia for pediatric cerebral magnetic resonance imaging by small doses of ketamine or nalbuphine administered just before discontinuing anesthesia. *Anesth Analg* 2006;**102**:1056–1061.
106. Bauchat JR, Higgins N, Wojciechowski KG, et al. Low-dose ketamine with multimodal postcesarean delivery analgesia: A randomized controlled trial. *Int J Obstet Anesth* 2011;**20**:3–9.
107. Unlugenc H, Ozalevli M, Gunes Y, et al. A double-blind comparison of intrathecal S(+) ketamine and fentanyl combined with bupivacaine 0.5% for Caesarean delivery. *Eur J Anaesthesiol* 2006;**23**:1018–1024.
108. Kathirvel S, Sadhasivam S, Saxena A, et al. Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. *Anaesthesia* 2000;**55**:899–904.
109. Togal T, Demirbilek S, Koroglu A, et al. Effects of S(+) ketamine added to bupivacaine for spinal anaesthesia for prostate surgery in elderly patients. *Eur J Anaesthesiol* 2004;**21**:193–197.
110. Frizelle HP, Duranteau J, Samii K. A comparison of propofol with a propofol-ketamine combination for sedation during spinal anesthesia. *Anesth Analg* 1997;**84**:1318–1322.
111. Saricaoglu F, Dal D, Salman AE, et al. Ketamine sedation during spinal anesthesia for arthroscopic knee surgery reduced the ischemia-reperfusion injury markers. *Anesth Analg* 2005;**101**:904–909.
112. Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 2005;**103**:147–155.
113. Welters ID, Feurer MK, Preiss V, et al. Continuous S-(+)-ketamine administration during elective coronary artery bypass graft surgery attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass. *Br J Anaesth* 2011;**106**:172–179.
114. Bartoc C, Frumento RJ, Jalbout M, et al. A randomized, double-blind, placebo-controlled study assessing the anti-inflammatory effects of ketamine in cardiac surgical patients. *J Cardiothorac Vasc Anesth* 2006;**20**:217–222.
115. Cho JE, Shim JK, Choi YS, et al. Effect of low-dose ketamine on inflammatory response in off-pump coronary artery bypass graft surgery. *Br J Anaesth* 2009;**102**:23–28.
116. Dale O, Somogyi AA, Li Y, et al. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. *Anesth Analg* 2012;**115**:934–943.
117. Neuhauser C, Preiss V, Feurer MK, et al. Comparison of S-(+)-ketamine- with sufentanil-based anaesthesia for elective coronary artery bypass graft surgery: Effect on troponin T levels. *Br J Anaesth* 2008;**100**:765–771.
118. Begec Z, Demirbilek S, Onal D, et al. Ketamine or alfentanil administration prior to propofol anaesthesia: The effects on ProSeal laryngeal mask airway insertion conditions and haemodynamic changes in children. *Anaesthesia* 2009;**64**:282–286.
119. Prossliner H, Braun P, Paal P. Anaesthesia in medical emergencies. *Trends Anaesth Crit Care* 2012;**2**:109–114.
120. Wang X, Chen Y, Zhou X, et al. Effects of propofol and ketamine as combined anesthesia for electroconvulsive therapy in patients with depressive disorder. *J ECT* 2012;**28**:128–132.
121. Bilgen S, Koner O, Ture H, et al. Effect of three different doses of ketamine prior to general anaesthesia on postoperative pain following Caesarean delivery: A prospective randomized study. *Minerva Anestesiol* 2012;**78**:442–449.
122. Sahin L, Sahin M, Aktas O, et al. Comparison of propofol/ketamine versus propofol/alfentanil for dilatation and curettage. *Clin Exp Obstet Gynecol* 2012;**39**:72–75.
123. Suzuki M, Haraguti S, Sugimoto K, et al. Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* 2006;**105**:111–119.
124. Ozyalcin NS, Yucel A, Camlica H, et al. Effect of pre-emptive ketamine on sensory changes and postoperative pain after thoracotomy: Comparison of epidural and intramuscular routes. *Br J Anaesth* 2004;**93**:356–361.
125. Safavi M, Honarmand A, Nematollahy Z. Pre-incisional analgesia with intravenous or subcutaneous infiltration of ketamine reduces postoperative pain in patients after open cholecystectomy: A randomized, double-blind, placebo-controlled study. *Pain Med* 2011;**12**:1418–1426.
126. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology* 2010;**113**:639–646.
127. Kwok RF, Lim J, Chan MT, et al. Preoperative ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. *Anesth Analg* 2004;**98**:1044–1049, table of contents.
128. Fletcher PC, Honey GD. Schizophrenia, ketamine and cannabis: Evidence of overlapping memory deficits. *Trends Cogn Sci* 2006;**10**:167–174.
129. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 1994;**51**:199–214.
130. Morgan CJ, Mofeez A, Brandner B, et al. Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: A dose-response study. *Psychopharmacology* 2004;**172**:298–308.
131. Kennedy RM, McAllister JD. Midazolam with ketamine: Who benefits? *Ann Emerg Med* 2000;**35**:297–299.
132. Moretti RJ, Hassan SZ, Goodman LI, et al. Comparison of ketamine and thiopental in healthy volunteers: Effects on mental status, mood, and personality. *Anesth Analg* 1984;**63**:1087–1096.
133. Cartwright PD, Pingel SM. Midazolam and diazepam in ketamine anaesthesia. *Anaesthesia* 1984;**39**:439–442.
134. Lilburn JK, Dundee JW, Nair SG, et al. Ketamine sequelae. Evaluation of the ability of various premedicants to attenuate its psychic actions. *Anaesthesia* 1978;**33**:307–311.
135. Fine J, Finestone SC. Sensory disturbances following ketamine anesthesia: Recurrent hallucinations. *Anesth Analg* 1973;**52**:428–430.
136. Cheong SH, Lee KM, Lim SH, et al. Brief report: The effect of suggestion on unpleasant dreams induced by ketamine administration. *Anesth Analg* 2011;**112**:1082–1085.
137. Erk G, Ornek D, Donmez NF, et al. The use of ketamine or ketamine-midazolam for adenotonsillectomy. *Int J Pediatr Otorhinolaryngol* 2007;**71**:937–941.
138. Dal D, Celebi N, Elvan EG, et al. The efficacy of intravenous or peritonsillar infiltration of ketamine for postoperative pain relief in children following adenotonsillectomy. *Paediatr Anaesth* 2007;**17**:263–269.
139. Hostetler MA, Davis CO. Prospective age-based comparison of behavioral reactions occurring after ketamine sedation in the ED. *Am J Emerg Med* 2002;**20**:463–468.
140. Blagrove M, Morgan CJ, Curran HV, et al. The incidence of unpleasant dreams after sub-anaesthetic ketamine. *Psychopharmacology* 2009;**203**:109–120.
141. Orlowski JP, Porembka DT, Gallagher JM, et al. Comparison study of intraosseous, central intravenous, and peripheral intravenous infusions of emergency drugs. *Am J Dis Child* 1990;**144**:112–117.

142. Von Hoff DD, Kuhn JG, Burris HA III, et al. Does intraosseous equal intravenous? A pharmacokinetic study. *Am J Emerg Med* 2008;**26**:31–38.
143. Malinovsky JM, Servin F, Cozian A, et al. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. *Br J Anaesth* 1996;**77**:203–207.
144. Green SM, Hummel CB, Wittlake WA, et al. What is the optimal dose of intramuscular ketamine for pediatric sedation? *Acad Emerg Med* 1999;**6**:21–26.
145. Sekerci C, Donmez A, Ates Y, et al. Oral ketamine premedication in children (placebo controlled double-blind study). *Eur J Anaesthesiol* 1996;**13**:606–611.
146. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. *Br J Anaesth* 1981;**53**:805–810.
147. Yanagihara Y, Ohtani M, Kariya S, et al. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharm Drug Dispos* 2003;**24**:37–43.
148. Panjabi N, Prakash S, Gupta P, et al. Efficacy of three doses of ketamine with bupivacaine for caudal analgesia in pediatric inguinal herniotomy. *Reg Anesth Pain Med* 2004;**29**:28–31.
149. Kumar P, Rudra A, Pan AK, et al. Caudal additives in pediatrics: A comparison among midazolam, ketamine, and neostigmine coadministered with bupivacaine. *Anesth Analg* 2005;**101**:69–73.
150. Martindale SJ, Dix P, Stoddart PA. Double-blind randomized controlled trial of caudal versus intravenous S(+)-ketamine for supplementation of caudal analgesia in children. *Br J Anaesth* 2004;**92**:344–347.

Supporting Information

The following supplementary material is available for this article:

Table S1. Prolongation of postoperative analgesia with caudal ketamine in pediatric patients, adapted from [80].

Table S2. Prolongation of postoperative analgesia with caudal S-(+)-ketamine in pediatric patients.