Recommendations on the safety and effectiveness of Ketamine for induction to facilitate advanced airway management in head injured patients in South Africa by pre-hospital professionals: A rapid review

STUDENT: Pierre Smit

Baccalaureus Technologiae – Emergency Medical Care

Student in Master's of Philosophy – Emergency Medicine

SMTPIE007

SUPERVISOR: Michael Gilbert McCaul

Biostatistics Unit, Centre for Evidence-based Health Care
Stellenbosch University

CO-SUPERVISOR: Prof. Lee Wallis

Head of Emergency Medicine – University of Cape Town

This study is in partial fulfilment of the Master's in Philosophy of Emergency Medicine degree

Declaration:

I, Pierre Christo Smit, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for degree purposes.

Signature: 

Date: 14 / 09 / 2016

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Abstract

Background

The South African 2006 Advanced Life Support and Emergency Care Practitioner protocols do not currently reflect the latest, best evidence-based practices for emergency care, specifically regarding induction agents in head injury patients. Recent evidence has challenged some preconceptions regarding the use and safety of Ketamine in head injuries. In response to this, the Health Professions Council of South Africa Professional Board for Emergency Care (HPCSA PBEC) has requested a review of the emergency care protocols.

Objectives

To determine the evidence of effectiveness and safety of intravenous/intraosseous (IV/IO) Ketamine as an induction agent for adult patients with traumatic brain injury, the authors aimed to determine the all-cause mortality at 30 days, adverse events/effects, morbidity and rate of successful intubation associated with ketamine administration, as compared to standard induction agents.

Research Question

What is the evidence of effectiveness and safety of IV/IO Ketamine in adult patients with head injury, for pre-hospital induction in advanced airway management, compared to standard therapy?

Methods

The review followed a tiered approach, where three different tiers of searches were performed for articles relevant to the research question. Two authors independently and in induplicate performed title, abstract and full-text review for each potentially included article, as well as critical appraisal of 3 CPGs found in the tier 1 searches. Tier 1 searched for Clinical Practice Guidelines (CPGs), tier 2 for Systematic Reviews (SRs) and tier 3 for Randomised Controlled Trials (RCTs) relating to the research question. No grey literature searches were performed, but reference lists of included articles were searched for relevant articles.

Main Results

The authors could not find any studies to include (CPGs, SRs or RCTs) in this review which would answer the research question. However, several articles were found which describe ketamine use in the Intensive Care Unit (ICU) and surgical patients with regards to intracranial pressure, cerebral perfusion pressure and general haemodynamic effects. Another article (RCT) was found which used ketamine as an induction agent compared to etomidate to facilitate intubation in critically ill patients. These articles provide some helpful insights as to ketamine's effectiveness and safety for induction to facilitate intubation in traumatic brain injury patients in the pre-hospital setting.

Conclusions

The authors could not make any recommendations regarding the research question, and the safety and effectiveness of ketamine for induction to facilitate intubation in adult traumatic brain injury remains unclear. A lack of empirical evidence at RCT level has led to substantial knowledge gaps regarding our understanding of Ketamine and its effects in traumatic brain injury patients.

Background

Ketamine, also referred to as Ketalar® or Brevinase®, is a synthetic medication first described in 1962 by Dr. Calvin Stevens. [1, 1] It is chemically related to phencyclidine (PCP), which it was designed to replace due to PCP's unappealing side-effect profile.[2] After being patented in Belgium in 1963, ketamine showed much promise as an anaesthetic agent and during 1965, began being used as a recreational drug by the public due to its potent hallucinogenic effects. [3] However, clinical data on ketamine was still sparse, and in the late 1960's saw its first real introduction into clinical medicine as an anaesthetic agent in the Vietnam War. [2]

Ketamine inhibits the N-Methyl-D-Aspartate (NMDA) receptor, causing a state of dissociative anaesthesia, whereby the user has near-complete sensory and motor dissociation from the cerebral cortex, without causing complete loss of consciousness. Essentially, a patient cannot perceive the world around them, nor is even aware of its existence, and is placed in a dream-like state where the brain remains active, but unable to cause any motor stimulation or be innervated by sensory stimulation. [4] Some of the beneficial effects of not causing complete loss of consciousness in anaesthetised patients are that respiratory function and airway reflexes remain intact at typical intravenous injection dosage. [5]

During its use in the Vietnam War, ketamine was regarded as being the "perfect" agent with regards to anaesthesia in haemodynamically unstable soldiers as it seemed to not decrease blood pressure as significantly, as compared to its benzodiazepine and/or opiate counterparts. [6] However, its side effects quickly became apparent as many patients anaesthetised with ketamine had significant delirium and "schizophrenia-like symptoms" upon waking. The term "emergence-delirium" was coined. [7] This was an expected phenomenon, as ketamine is closely related to PCP which has the same emergence effects; these effects are successfully were treated with the concomitant administration of a gamma aminobutyric acid (GABA) agonist, such as benzodiazepines. [8] However, these effects were not as pronounced as with PCP and ketamine was still considered a viable replacement.

Due to emergence delirium, ketamine made a significant move into veterinary medicine where this factor was not considered as unappealing as in human patients. [9] Animal models were used to further research the effects, side-effects and toxic-effects of ketamine to better the clinical understanding of the medication. [9] During this period, researchers described the secondary pharmacological effects of the drug, for which it is so well known today. Apart from the effects on

the central nervous system, ketamine has also been known to have significant cardiovascular effects, which have been the subject of much debate in recent years [5]. It has a directly negative inotropic effect, decreasing ventricular contractility, and has little effect on peripheral vascular resistance, thereby seemingly reducing systemic blood pressure. [6] However, it has positive chronotropic effects and causes positive sympathetic stimulation which leads to catecholamine release and an increase in cardiac output and blood pressure. The net result is an increase or maintaining of the systemic blood pressure. Thus, in haemodynamically unstable and critically ill patients, ketamine may be more beneficial compared to opioids and benzodiazepines, which are known to decrease systemic blood pressure when given in doses sufficient to cause anaesthesia. [6]

Ketamine also causes increased cerebral blood flow, which has led to the belief that it has the potential to increase intra-cranial pressure (ICP) in patients with traumatic brain injury (TBI). [10–14] As a result, it was contra-indicated as an anaesthetic agent for intubation in patients with TBI. There is a significant lack of clinical practice guidelines and society statements on the use of Ketamine in TBI. However, recent publications have refuted this, [15–20] showing that it increases cerebral blood flow and reduces cerebral oxygen demand, [21–24] thereby improving the supply/demand ratio. Secondary brain injury due to hypotension and hypoperfusion in TBI has been associated with higher morbidity and mortality as compared to the transient increases in cerebral perfusion pressure (CPP) associated with ketamine administration. Thus, the haemodynamic stability of ketamine is attractive for administration in the critically ill TBI patient; however, the evidence for use in these settings remains unclear. [21–24]

Endotracheal intubation is considered the gold standard of securing the airway in severe TBI patients. [25] It protects the airway, provides a conduit for ventilation (either manual or mechanical), and enables patients to be sedated as a neuroprotective intervention until definitive treatment can be provided. [25] However, the ideal induction agent for facilitating intubation in this patient population has not been identified. Etomidate and ketamine are popular choices in the South African pre-hospital environment, but they both have a significant side-effect profile which makes it difficult to establish which is superior.[21] South Africa is a low-to-middle income country where accidents and injuries form a significant proportion of the country's burden of disease. [26] Therefore, TBI is a common occurrence in most prehospital and emergency centre settings across the country. An induction agent which is cheap, readily available and accessible, safe and effective is the ideal agent

in a setting such as South Africa due to challenges in resource constraints and access to tertiary care. [26]

Etomidate has been described as causing relative adrenal insufficiency, which may introduce more risk to TBI patients as hypotensive episodes (caused by decreased catecholamine production) may lead to hypoperfusion of the injured brain. However, ketamine maintains haemodynamic stability which reduces the risk of hypotension and hypoperfusion of the brain and has also been shown to have some neuroprotective effects which may protect against hypoxic, ischemic, mechanical and chemical neuronal damage.[23] These factors may make ketamine the preferred agent for induction of TBI patients as it may reduce the mortality and morbidity in the acute emergency TBI patient. However, clinicians have been weary of ketamine due to a perceived dogma that ketamine raises the ICP, which may be detrimental in severe TBI patient. [21]

The publications warning of ketamine's use in traumatic brain injury were largely based on theoretical arguments in the 1970's, as few studies which had any clinical arguments were available at the time. Most of the publications claiming harm associated with ketamine anaesthesia in TBI patients performed their studies on participants with known cerebrospinal fluid abnormalities and blockages. [11,12,15]

Thus, the results have most likely been biased and do not reflect the true potential and safety of ketamine. In the past decade, interest in ketamine had resurfaced in evidence-based medicine and publications aimed at disproving ketamine's harmful effects on ICP have become numerous. [15,17–24] Thus, a rapid review on the current evidence of ketamine use in adult patients in intubation TBI can establish whether ketamine may be useful as an anaesthetic agent in the pre-hospital environment.

Motivation for Research

The South African 2006 Advanced Life Support (ALS) and Emergency Care Practitioner (ECP) practitioner protocols do not currently reflect the latest, best evidence-based practices for emergency care, specifically regarding induction agents in TBI patients. The HPCSA PBEC has recently requested a review of the emergency care protocols. Thus, a rapid review will be useful, to synthesize the latest evidence in order to update the protocols, inform policy makers, guideline developers and guide clinicians [27] regarding the safety and effectiveness of intravenous/intraosseous (IV/IO) ketamine for induction in the pre-hospital setting in South Africa.

Research Question

What is the evidence of effectiveness and safety of IV/IO ketamine for pre-hospital induction in advanced airway management in adult patients with head injury, with regard to mortality and morbidity, compared to standard therapy?

Objectives

Primary Objective

1. To determine the evidence of effectiveness and safety of IV/IO ketamine as an induction agent for adult patients with head injury for use by pre-hospital professionals in advanced airway management compared to standard therapy in the South African setting.

Secondary Objectives to Inform the Primary Objective

1. To determine all-cause mortality of patients with head injuries given ketamine for induction at one month (30 days) compared to standard therapy
2. To determine adverse events/effects associated with the administration of ketamine in induction of patients with head injury compared to standard therapy
3. To determine the morbidity associated with the administration of ketamine for induction of patients with head injury compared to standard therapy
4. To determine the effectiveness of IV/IO ketamine, by measuring the rate of successful induction and endotracheal intubation, respectively, of patients with head injury using ketamine as induction agent compared to standard therapy for induction.

Methods

We performed a rapid review of the available literature on ketamine's effectiveness and safety as an induction agent in patients with TBI in the pre-hospital setting, compared to standard therapy. Rapid reviews involve the same processes associated with systematic reviews, whereby all available evidence is sought regarding a particular topic or research topic. However, rapid reviews streamline some of the traditional systematic review methods in order to synthesize evidence in a shorter timeframe. [28]

This review has followed a tiered approach, where high-quality Clinical Practice Guidelines (CPGs) [29] form the first tier of studies which were sought for inclusion, followed by Systematic Reviews (SRs)

and finally, Randomised Controlled Trials (RCTs). If the search strategy could identify a study or studies which would answer the research question in a higher tier, the searches would not have been continued to the lower tier/s. However, as no studies were found in the first 2 tiers which would answer the research question, all 3 tiers of searches were performed.

Criteria for Considering Studies for this Review

Types of Studies

First Tier - Clinical Practice Guidelines

As defined by the Institute of Medicine, clinical guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.[30] They are traditionally based on one or more high-quality SRs and undergo intensive review, which make them such a sought-after source of evidence-based recommendations. CPGs are based on three important characteristics: an established evidence base, public and stakeholder consultation and translating recommendations into practice.

High quality CPGs provide an excellent summary of evidence with contextualisation for a specific setting. Recommendations/data from high quality CPGs allow us to answer the research question rapidly as they should include evidence from SRs and RCTs for an intervention question.

Second Tier - Systematic Reviews

SRs follow rigorous methods to systematically search for, appraise and synthesise research evidence for a particular research question. [31] It is the explicit and systematic approach that distinguishes systematic reviews from traditional reviews and commentaries.[32] A systematic review often identifies several studies addressing the same question. Thus, if the studies' methodologies and sample populations are comparable, it would be reasonable to pool the findings in a quantitative (e.g. meta-analyses) or qualitative (e.g. narrative review) synthesis. The synthesised results can then be used by policy makers and guideline developers to influence decision-making by clinicians. [33] Due to their explicit and rigorous methods to produce synthesised evidence regarding the effectiveness of an intervention, systematic reviews formed the second tier of studies sought for inclusion.

Third Tier - Randomised Controlled Trials

RCTs are considered the gold standard of evaluating the effectiveness of interventions in primary research. No other research methodology provides the same level of reliable evidence on the effectiveness of an intervention, as the processes used during the conduct of an RCT minimise selection bias and confounding factors which may influence the results. RCTs were the third tier of studies sought for inclusion in this review.

Types of Participants

Adults with TBI who require induction and intubation in either the pre-hospital or emergency department settings. TBI was defined as per the included studies' criteria for TBI, but should have contained the following common indicators: The patient's history/mechanism of injury or symptoms suggesting head injury, [34] or a Glasgow Coma Scale (GCS) ≤13/15.[35]

In this review the authors included both the prehospital and emergency centre as primary population groups in the searches, as the key demographic of interest was TBI in the acute emergency setting. Although the data may not vary much between these two groups in the key aspects, a distinction is made between them, and patients who have been admitted to wards (surgical or recovery) and the ICU, as the clinical setting in these environments are fundamentally different from the emergency centre and prehospital environment.

Types of Interventions

Ketamine administration as an anaesthetic agent to facilitate endotracheal intubation in the pre-hospital setting. Proprietary names of Ketamine which were specified for inclusion include Ketamine, Ketalar™ and Brevinase™. Other proprietary names have not been included in the search strategy.

Types of Comparators

In this review, Ketamine as an anaesthetic agent to facilitate endotracheal intubation in patients with TBI was compared to "standard therapy", where standard therapy refers to the commonly used induction modalities and medications currently available in the South African Pre-hospital environment. This includes etomidate, midazolam and the midazolam/morphine cocktail. In the searches performed for this review, it was accepted that doses among these various medications may not be uniform, or similar to what is prescribed in the South African protocols. As an example, below is an outline of standardised dose ranges for the anaesthetic agents commonly used in the South African Pre-hospital environment.

- Etomidate: 0.2 - 0.3 mg/kg (actual body weight) [36–39]
- Ketamine: 1 - 3 mg/kg (ideal body weight) [36,39,40]
- Midazolam: 0.1 - 0.3 mg/kg (actual body weight) [36,39,40]
- Morphine and Midazolam (any dose) (actual body weight)

For the purposes of this review, the search was not limited to studies which only compare Ketamine to the above medications, but has included studies that use other medications to induce patients for intubation in the pre-hospital environment as well.

Types of Outcome Measures

For each tier of studies for inclusion (CPGs, SRs and RCTs) the outcomes, as defined below, would have been extracted:

- For CPGs, recommendations and evidence matrices that answer the research question would have been extracted and, if reported, the pooled data (meta-analysis or network meta-analysis) or individual effects (e.g. for a single RCT) would also have been extracted. If reported, summary of findings (SoF) tables and evidence quality grading matrices would also have been sought and extracted.
- For SRs, the pooled data (meta-analysis or network meta-analysis) per outcome or individual effects (e.g. for a single RCT) will be extracted if reported. If reported, SoF tables and evidence quality grading matrices would also have been extracted.
- For RCTs, the below outcomes were searched for directly.

Primary Outcomes

All-cause mortality at one month

Secondary Outcomes

1. Adverse effects. An adverse event was defined as an event for which a causal relationship between the intervention and the event was a reasonable possibility (e.g. convulsions, unexplained delirium and emergence delirium)
2. Morbidity associated with the administration of Ketamine for induction of patients with head injury compared to standard therapy
3. Rate of successful endotracheal intubation of patients with TBI using Ketamine as induction agent compared to standard therapy for induction

Search Methods

Electronic Searches

The electronic searches were performed in the databases mentioned below for each respective tier of inclusion, i.e. CPGs, SRs and RCTs. The relevant search strategies are outlined in *Appendix 1*. For each tier of inclusion, a separate search strategy was developed as the databases for RCTs, CPGs and SRs all have different search keywords, characteristics and MeSH (Medical Subject Headings) terms. For example, PubMed uses MeSH terms, whereas Scopus does not. The "English" language filter was applied to all electronic searches once the search strategy has been entered into the appropriate database, but no publication date filters were added. The search strategies used in this review were developed and validated in conjunction with an information and searching specialist at University of Cape Town health sciences library.

Clinical Practice Guidelines

Clinical Practice Guidelines (CPGs) pertaining to the research question were searched for on the 22nd September 2015 using the search terms: "Ketamine OR Ketalar OR Brevinase AND Head Injur* OR Brain Injur* OR traumatic brain injur* OR Head trauma", or a variation thereof in databases which did not recognize the asterisk function in searches, in the following databases:

- Scottish Intercollegiate Guidelines Network (SIGN)
- National Institute for Healthcare Excellence (NICE)
- New Zealand Guidance Group (NZGG)
- National Health and Medical Research Council (NHMRC)
- Trip
- Scopus
- Ebscohost
- Pubmed

See: appendix 1.1 for specific CPG search strategies

Systematic Reviews

Systematic reviews were searched for on the 1st October 2015 using the search term "Ketamine AND (Head Injur* OR Brain injur*)" or an appropriate adaptation in databases which do not recognize the asterisk function in search terms, in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL)

- Scopus
- PubMed

See: appendix 1.2 for specific SR search strategies

Randomised Controlled Trials

RCTs were searched for on the 20th of January 2016 using the search terms as defined in appendix 1.3, in the following databases:

- Pubmed
- Medline
- Scopus
- Cochrane CENTRAL Library

See: appendix 1.3 for specific RCT search strategies

Searching Other Sources

Reference lists of included studies (CPGs, SRs, and RCTs) were searched for identifying other potential studies for inclusion. The authors have not searched for 'grey literature' and/or unpublished works, due to operational time constraints. One study author, Brian Driver [41], was contacted to obtain a full-text article, but the study had not yet been completed by the time as this review was completed. This study and its potential future implications for this review are discussed further below. Trial registries have not been searched

Data Collection and Management

Selection of Studies

After the search results were produced, EndNote reference management software was used to remove any duplicate records. Two review authors (PS and MM) independently and in duplicate screened titles and abstracts to remove obviously irrelevant reports and retrieve the full-text of potentially relevant reports. PS and MM resolved any disagreements regarding inclusion or exclusion of a study by discussion, and if resolution was not obtained, consultation with an independent third party (AL) was the planned solution. However, consultation with an independent third party was never required as all disagreements were resolved with discussion. Neither author was blinded to the names of the study authors, institutions, journal of publication nor results, as this practice had uncertain benefit in protecting against bias. [42] Three flow diagrams were created to report the process of inclusion and exclusion of studies, and delineate the numbers of studies excluded during the process. These can be found in-text under the 'Results' section. A table of excluded studies was

created from the full-text articles deemed not for inclusion by the review authors (PS & MM), and included a brief explanation as to the reason for exclusion. We reported any included studies in the included studies table and excluded studies in excluded studies table.

Data Extraction and Management

The two reviewers planned to independently and in duplicate extract data from included studies using a pre-specified data extraction form for CPGs, SRs or RCTs respectively. The data extracted would have relied on pre-specified outcomes which pertain to the research question and the relevant objectives.

The following information would have been collected from an included study:

- Study Particulars (Review author contact details, study or report registration ID, citation and name/s of person extracting data)
- Eligibility of Inclusion (Confirmation that study is eligible for inclusion as per protocol and does not meet criteria for exclusion)
- Methods (study aim/s, design, duration)
- Participants and Setting (study population and location, recruitment method, inclusion and exclusion criteria, informed consent obtained where applicable, number of participants in each arm (if RCT) or number of included participants in pooled analysis (if SRs or CPG), rural or urban setting, developing or developed country, subgroups measured, subgroups reported)
- Interventions and comparators (Ketamine hydrochloride or other preparation, dosage, route of administration, time of medication administration, place of administration)
- Outcome measures coupled with results (outcome definition/name, person measuring or reporting, all-cause mortality at 30 days or longer where available, adverse effects, morbidity, comorbidities, success rates of intubation)
- Results (continuous variables (mean or mean difference) of outcome data with measures of variability (standard deviation), dichotomous data such as total number of events in each arm and numbers of participants (if RCT), meta-analysis results or network meta-analysis results (SRs), clinical practice recommendations from CPGs with summary of findings tables or equivalent measures of effect measure quality)
- Applicability (populations included and excluded, disadvantaged groups, applicability to developing countries)

Critical Appraisal

Clinical Practice Guidelines

To appraise CPGs the Appraisal of Guidelines for Research and Evaluation II (AGREE II) appraisal tool was used. [43] The purpose of AGREE II is to provide a framework to assess the quality of guidelines, provide a methodological strategy for the development of guidelines; and inform what information and how information ought to be reported in guidelines. The AGREE collaboration has defined the quality of guidelines as "the confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice". [43]

The AGREE II tool has six domains which all appraise difference facets of the guideline document. These six domains are split (not uniformly) into 23 items which require appraisal by the appraiser/s. Upon completion of the 23 items (and resultantly, the 6 domains) and overall assessment of the guideline will be made by all appraisers, and a final score assigned to the guideline document. The final score will determine the guideline's overall quality, based on the score itself and the subjective judgements of the appraiser/s. The score provides a subjective estimate of the guideline quality, as no minimum acceptable score or acceptable score range has been defined by the AGREE II authors to date.

A guideline would have been considered high-quality if the AGREE II score is considered acceptably high by the appraisers in this review (PS & MM), when appraised independently and in duplicate . If there was a disagreement between the two review authors (PS & MM) which could not be resolved through discussion, then the independent third party (AL) would have been consulted for resolution. A guideline which did not meet the desired requirements to be considered high-quality (above 60% adherence to AGREE II items) was assigned a low quality rating and excluded from the study.

Systematic Reviews

To appraise systematic reviews, the Assessment of Multiple Systematic Reviews (AMSTAR) appraisal tool would have been used. AMSTAR is a tool specifically designed to appraise systematic reviews of interventions and is an 11-item questionnaire that is used to assess their methodological quality.[44] It provides a framework for the appraisal of a systematic review's methodological quality, validity (both internal and external) and risk of bias.

To apply AMSTAR, each systematic review was to be appraised by two reviewers (PS and MM) and judged against the criteria set out in the appraisal tool. AMSTAR determines the methodological quality of a systematic review by assessing the presence of:

- an a priori design;
- duplicate study selection and data extraction;
- a comprehensive literature search;
- the use of status of publication as an inclusion criterion;
- a list of included/excluded studies;
- characteristics of included studies;
- documented assessment of the scientific quality of included studies;
- appropriate use of the scientific quality in forming conclusions;
- the appropriate use of methods to combine findings of studies;
- assessment of the likelihood of publication bias; and
- documentation of conflict of interest

Upon completion of the appraisal questionnaire, a point is awarded for each of the 11 items which have been satisfactorily addressed in the review being appraised. A point of 0 is assigned to items which are not met, unclear or not applicable. Thus, a maximum score of 11 out of 11 is a systematic review which likely has minimal risk of bias, and a minimum score of 1 out 11 is a systematic review which almost certainly has one or several sources of bias. [44]

An overall score relating to review quality is then calculated (the sum of the individual item scores). AMSTAR characterises quality at three distinct levels: 8 to 11 is high quality, 4 to 7 is medium quality, and 0 to 3 is low quality. The principals of the AMSTAR tool can be used to demonstrate aspects of systematic review methodology that influence the overall quality of a review. [45] Ideally, this review aims to only include studies which fall within the high quality category. However, in some cases, if better quality studies could not be found for inclusion, studies with medium quality would have been included.

Randomised Controlled Trials

The Physiotherapy Evidence Database Scale (PEDro) [46] is a tool to appraise the quality of an RCT. It consists of 11 items that are designed to test the external and internal validity, as well as the statistical interpretability of an RCT. The first item decides its external validity, and the other 10

items are summed to give a score out of 10 for the particular RCT. For this review, a PEDro score of more than 5 out of 10 would have been the benchmark for inclusion.

The Cochrane Collaboration's 'Risk of Bias' appraisal tool would also have been used to appraise RCTs in terms of their stated or perceived risk of bias. The Risk of Bias tool has six domains, which assess the factors identified as being likely indicators of bias in RCTs. RCTs will be appraised independently and in duplicate by both review authors (PS and MM) and the following domains addressed: Sequence Generation, Allocation Concealment, Blinding (blinding of participant and personnel, blinding of outcome assessors), incomplete outcome data, selective outcome reporting and other risks of bias.[42]

Data Synthesis and Evidence Synthesis

Clinical Practice Guidelines

CPGs which have gone through full-text review and have been included would undergo critical appraisal by using AGREE II. Outcomes which met the requirements of this review would have been adapted, adopted or contextualised to the outcomes as specified in this review. The data would then have been synthesised narratively to answer the research question and provide recommendations for the effectiveness and safety of Ketamine as an anaesthetic agent in patients who require intubation in the prehospital setting. Decisions to adopt, adapt or contextualise [47] guidelines recommendations would have been made in conjunction with MM and AL.

Systematic Reviews

If systematic reviews were found which answer the research question and have been appraised to be of sufficient quality to be included in the review, their results and recommendations would have been synthesised based on the type of data and outcomes found. The results from SRs and RCTs would have been graded according to the National Health and Medical Research Council (NHMRC) Body of Evidence Matrix (BEM) for rapid reviews.[48]

Randomised Controlled Trials

The data obtained from RCTs would have been analysed in one of two ways, either through narrative review, or if possible, meta-analysis. Narrative synthesis would attempt to rank interventions based on study reported effect measures and risk of bias assessments and would describe study characteristics as it would have been seen in the table of included studies. Meta-analysis would have been performed if multiple RCTs were found which are methodologically and clinically similar, with a chi^2 or I^2 statistic which was not indicative of significant heterogeneity. We would have used a fixed-

effect meta-analysis if studies were estimating the same treatment effect (no statistical heterogeneity) and a random-effects meta-analysis if studies showed substantial heterogeneity (I^2 >80%). Subgroup analysis would have been performed if appropriate (defined in the subgroup analysis section). Since it is possible that RCTs comparing multiple combinations of treatment interventions (e.g. ketamine vs morphine vs etomidate, etc.) may have been found, a network meta-analysis (NMA) could have been performed. As network meta-analysis is an advanced form of evidence synthesis this statistical aggregation might have been outside of the scope of this dissertation and would only have been performed if time and resources considerations could be met. If NMA was warranted but not performed, this would then have been explicitly stated in the results section. If NMA was performed, standard NMA methods would have been used as defined by the Cochrane Multiple Interventions Methods Group (http://cmimg.cochrane.org/).

Evidence generated from synthesised RCTs would have been graded according to the National Health and Medical Research Council (NHMRC) Body of Evidence Matrix (BEM) for rapid reviews as mentioned previously. If data from both SRs and RCTs were available then both would have been used in the NHMRC BEM.

Sub-group Analysis

We planned to conduct sub-group analysis as recommended by Deeks 2001[49] to investigate differences between two or more subgroups. Subgroup analysis would have been performed if there were adequate studies to justify such analysis.

Pre-defined sub-group characteristics included:

- Medical Practitioner compared to paramedic
- Rapid Sequence Intubation (RSI) versus non-RSI (paralytic administered vs. no paralytic administered)
- Low-to-middle income countries (LMIC) and High-income countries (HIC)

Results

Results of the Searches

Clinical Practice Guidelines - Study Flow Diagram

Figure 1 details the process followed for the CPG searches, full-text review and AGREE II appraisals. 86 records were found (85 records identified through database searches and 1 record identified

through other sources). Of those, 69 records were excluded in the title/abstract screening. The remaining 17 potential included articles then underwent full-text review and all 17 records were excluded, with reasons for the exclusion provided in Table 1.1: Tier 1 table of excluded studies.

Three of the CPGs, (Green, et al. [50], Mayglothling, et al. [51] and Jensen, et al. [52]) were appreciably close to the research question, and although were excluded from the review, the authors performed critical appraisal of them using AGREE II as an indication of the quality of guidance currently available for healthcare providers regarding the research question. All three CPGs scored low on the AGREE II assessment, and were determined to be of a low quality. This indicates that the guidance currently available to healthcare providers regarding this topic is very poor. The AGREE II scores obtained by the 3 CPGs can be found in Appendix 2.

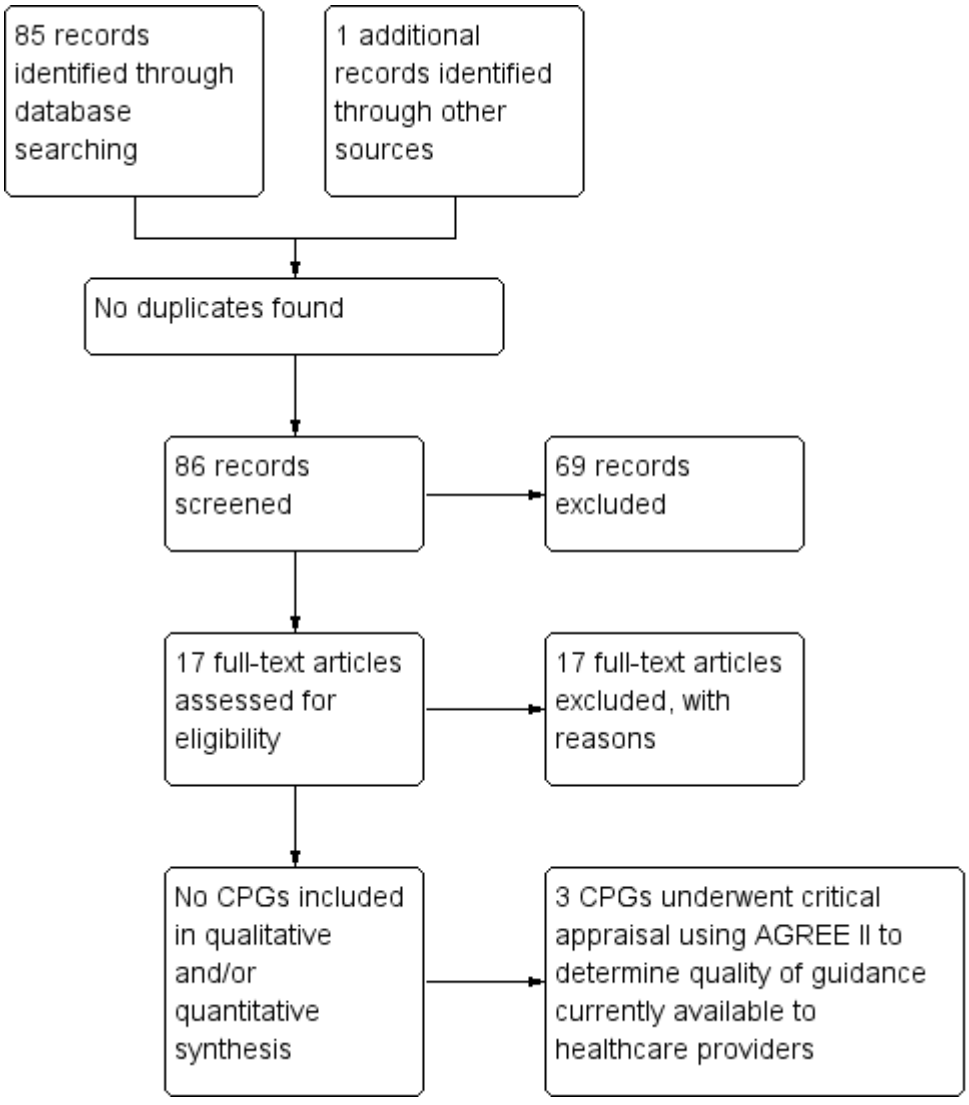

Figure 1: Clinical Practice Guidelines Flow Diagram (Tier 1)

Systematic Reviews - Study Flow diagram

Figure 2 details the process followed for the SR searches and full-text review. 80 records were found (82 records identified through database searches and 3 records identified through other sources, with five records which were duplicates removed). Of those, 59 records were excluded in the title/abstract screening. The remaining 21 potential included articles then underwent full-text review and all were excluded, with reasons for the exclusion provided in Table 1.2: Tier 2 table of excluded studies.

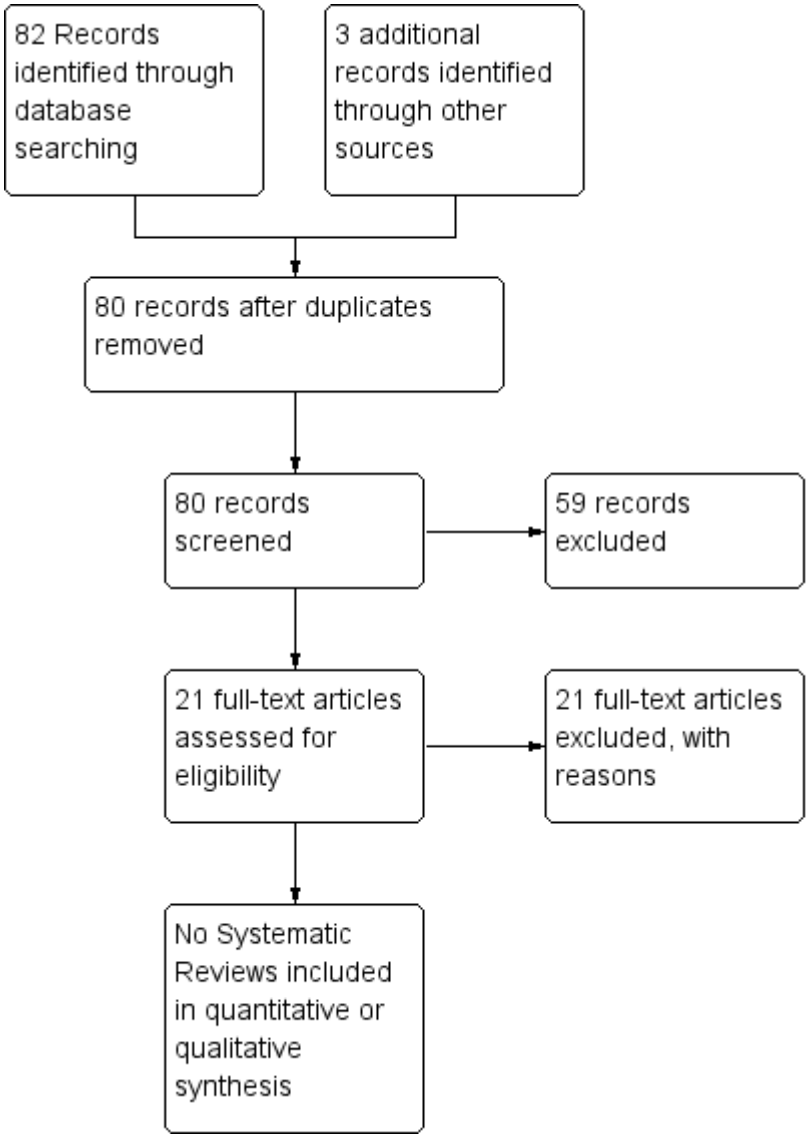

Figure 2: Systematic Review Flow Diagram

Randomised Controlled Trials - Study Flow Diagram

Figure 3 details the process followed for the RCT searches and full-text review. 385 records were found (403 records identified through database searches, but 18 records were duplicates and removed). Of those, 376 records were excluded in the title/abstract screening. The remaining nine potential included articles then underwent full-text review and all were excluded, with reasons for the exclusion provided in Table 1.3: Tier 3 table of excluded studies.

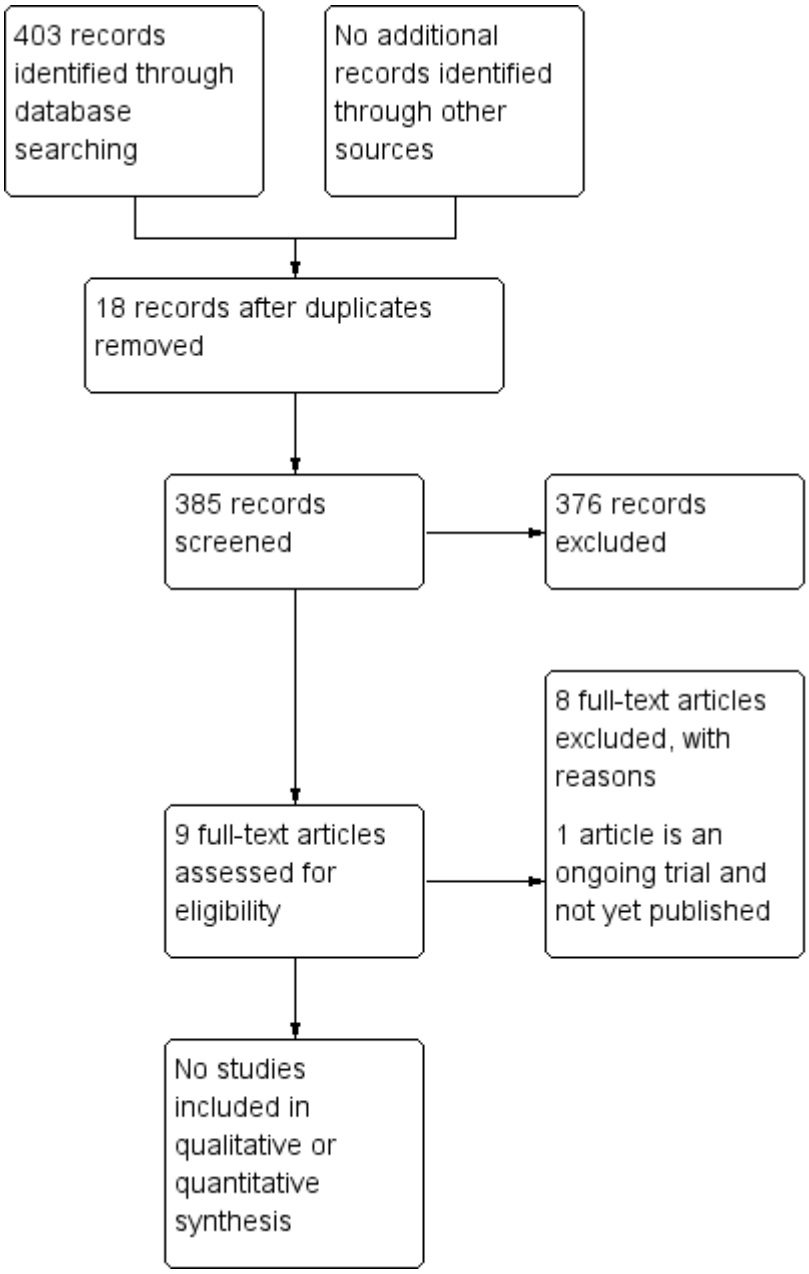

Figure 3: Randomised Controlled Trial Flow Diagram

Description of Included Studies

The authors could not find any studies to include (CPGs, SRs or RCTs) in this review which would answer the research question.

Description of excluded studies

References to the excluded studies (CPGs, SRs and RCTs) can be found below, under the heading 'References to Excluded Studies'. The excluded studies with their respective reasons for exclusion are described in Tables 1.1, 1.2 and 1.3, whereas Tables 2.1, 2.2 and 2.3 contain summaries of the excluded studies which were most relevant to the review's research question. It includes comments by the author describing its relevance to the research question, as well as to healthcare providers in the South African pre-hospital or emergency department settings.

Description of Quality of Reporting

AGREE II

The AGREE II assessment was performed as per the guidelines set out in the AGREE II appraisal tool manual. [43] Appendix 2 reflects the aggregate scores (MM and PC) obtained by each CPG, for each respective domain, as well as a graphical representation of the aggregate scores obtained by each of the 3 CPGs on which AGREE II was performed. AGREE II was used as a guide to determine which guidance documents were 'true' CPGs, as many articles which are published as CPGs tend not to be true CPGs. E.g. an end-user document for guidelines on seizure management, but which has not been performed using the methods and rigour required with a true CPG.

AMSTAR

As all systematic reviews found in the searches were excluded at full-text review, no systematic reviews were appraised using AMSTAR.

PEDRO and Cochrane Risk of Bias (ROB)

As all randomised controlled trials found in the searches were excluded at full-text review, no randomised controlled trials were appraised using PEDRO and Cochrane Risk of Bias (ROB) tool.

Ongoing trials/studies

An RCT of great interest to the authors is currently underway by Driver, et al.[1] They are comparing ketamine to etomidate for rapid sequence intubation in the emergency centre on all adult, non-prisoner patients who present to an urban level 1 trauma centre. Their research outcomes match our review's very closely, as they are comparing mortality, intubation success, intubation complications and short-term safety outcomes between ketamine and etomidate in these patients.

They presented their preliminary findings at a conference and found no difference in any of the study outcomes between the two groups. This trial is registered at clinicaltrials.gov: NCT01823328.

The study authors were contacted to obtain a full-text, if it were available. But, as the study has not been completed by the time of submission of this review, it could not be included. The principal investigator of the RCT has informed the authors that they plan to do a sub-group analysis of TBI patients in their study, which would be of great value to our review.

Effects of the Intervention

As no studies were included in this review, the authors are uncertain regarding the effectiveness and safety of Ketamine for induction to facilitate intubation in adult TBI patients and are thus unable to make recommendations due to a lack of empirical evidence or guidance for the pre-hospital setting.

Discussion

We did not find any CPGs, SRs or RCTs which answer the research question regarding the safety and effectiveness of IV/IO ketamine for induction to facilitate intubation in adult TBI patients in the pre-hospital setting. The effect of ketamine on mortality, morbidity, adverse effects and intubation success rates in this patient population is not yet clear. However, several articles were found which describe ketamine use in Intensive Care Unit (ICU) and surgical patients with regards to intracranial pressure, cerebral perfusion pressure and general haemodynamic effects. [49-54] Another article (RCT) used ketamine as an induction agent compared to etomidate to facilitate intubation in critically ill patients. [49] Although these articles would be excluded as they do not match our population of interest (TBI), intervention, comparator and/or outcome, they may provide some helpful insights as to ketamine's effectiveness and safety for induction to facilitate intubation in TBI patients in the pre-hospital setting. These articles are discussed below. The most relevant articles regarding the research question which were found in the tier 1, tier 2 and tier 3 searches, are narratively summarised in Tables 2.1, 2.2 and 2.3, respectively.

In total, the authors screened 551 potentially relevant papers (86 under tier 1, 80 under tier 2 and 385 under tier 3), screened their reference lists and contacted an author of an RCT [41] to obtain the full-text. It is possible that the authors may have missed a potentially relevant article due to some limitations of the study design, such as the exclusion of grey literature, articles published in languages other than English and the exclusion of studies which did not have the desired type/methodology, such as cohort, literature review, case/control and case series studies. However,

due to the thorough search strategies and the use of a tiered approach it is highly unlikely that a relevant article published in English was missed.

Table 2.1 provides a summary of CPGs on ketamine which may provide some insights into the intervention effect. Green, et al.[50] provided an argument for ketamine use in TBI patients, and have subsequently removed TBI as a relative contraindication for ketamine administration from their 2011 update of the original guideline published in 2004. They stated that newer evidence suggests that ketamine does not seem to cause clinically significant increases in intracranial pressure, and that increases are likely to be minimal and not sustained if they do occur in patients with normal ventilation. The resulting cerebral vasodilation caused by ketamine may in fact improve cerebral perfusion, and thereby improve outcomes of TBI patients. Also, given the lack of any supportive evidence that ketamine may cause harm to the acutely traumatised brain, the historical contraindication to its use seems unsupported.

This thought is shared by the authors of this review, as the clinical evidence available does not seem to substantiate that ketamine causes harm to the acutely injured brain. The historical publications [10–14,16] which led to the contraindication of ketamine for TBI patients, based their studies on patient populations which had their cerebrospinal fluid (CSF) flow naturally or artificially blocked. As ketamine causes cerebral vasodilation, the brain would not be able to compensate for the resulting rise in intracranial pressure by shunting CSF away from the brain, causing an increase in intracranial pressure. Thus, these studies were inherently flawed, as they proved that ketamine could cause a rise in intracranial pressure, but only if the patient's CSF flow is disrupted. Thus, in a normal patient population where CSF flow is, or is assumed to be, normal, these effects would likely not occur, as is shown by recent publications on ketamine where no, or minimal intracranial pressure increases (and in some cases, decreases) have been found. [16, 18-24]

Mayglothling et al.[51] stated that "*there are no convincing studies evaluating the effects of ketamine on ICP when used as an induction agent.*" Although the authors stated that etomidate is currently the preferred induction agent for rapid sequence intubation in many centres (due to its haemodynamic stability, rapid onset and familiarity with its use), they emphasised that it is not without side-effects. However, care should be taken in using etomidate for induction of trauma patients, as the adrenal insufficiency sometimes caused by etomidate may lead to worse patient outcomes. Jensen et al [50] recommend that ketamine be considered for induction for RSI in haemodynamically unstable patients, and be avoided (or used with extreme care) in patients with

ischemic heart disease. However, the authors were silent regarding ketamine use in patients with TBI.

The overall reporting quality of CPGs was relatively poor, considering that for an article to be considered a true CPG, reporting quality should be exemplary and supplemented by a systematic review of the literature. The AGREE II Collaboration [43] has outlined several reporting quality indicators which should be met for a CPG to be considered of a high quality. However, the CPGs found in the tier 1 search were considered low quality according to the AGREE II tool. This, in addition to the author's assessment of the CPGs found, have led to their overall exclusion from the review. Other than Green et al., no other CPG found made recommendations on the use of ketamine as an induction agent to facilitate intubation in TBI patients. This is likely as a result of the paucity of evidence and/or significant controversies regarding the topic.

Table 2.2 provides a summary of SRs on ketamine which may provide some insights into the effectiveness and safety of ketamine for induction of TBI patients. Cohen et al.[51] was a systematic review published in 2015 where the authors wanted to establish whether ketamine raises intracranial pressure or worsens neurological outcomes. Their review included studies which reported human data on the effect of intravenous ketamine used as an infusion or bolus dose in patients who had previously been intubated or who were being intubated at data collection. The majority of the articles they included in their review were of TBI patients in the intensive care unit.

They found conflicting results amongst the included studies, with some reporting increases in intracranial pressure and others a decrease in intracranial pressure post-administration. However, neither was sustained long enough to be considered clinically significant. The authors stated that the available data suggests that ketamine, compared to other induction agents commonly used to intubate adult patients in the emergency department, does not have an adverse effect on intracranial or cerebral perfusion pressures, neurologic outcomes or mortality. However, their review was limited by a lack of large, well-designed and -conducted randomised controlled addressing the topic, and they based their results on patients not commonly found in the emergency department (i.e. intensive care or surgical patients).

There is a lack of large, pragmatic, well-conducted randomised controlled trials to provide an evidence base for the use of ketamine in TBI patients. Both CPGs and SRs are inherently reliant on scientifically robust study designs (such as RCTs) to strengthen their evidence base and

recommendations for an intervention. When one considers the grading of evidence using the National Health and Medical Research Council Evidence Grading Matrix [48], a high quality RCT with low risk of bias can produce a level 1 evidence base for a particular recommendation, which is the highest level. This emphasises the need for high quality RCTs with low risk of bias regarding this topic, as systematic reviews and clinical practice guidelines based on poor quality evidence, will yield poor quality recommendations to inform practice.

Wang et al.[54] was a systematic review published in 2014 where the authors wanted to establish whether ketamine had an effect on intracranial pressure (ICP) and other cerebral hemodynamics, to determine whether ketamine was safe for patients with hemodynamic instability and TBI. They performed meta-analyses for intracranial pressure, mean arterial pressure and cerebral perfusion pressure, respectively. The first meta-analysis showed that ketamine led to no difference in ICP as compared to opioids (mainly sufentanil and fentanyl) [MD=1.94; 95% CI, -2.35, 6.23. I2 = 85%; P = 0.38] and followed a random-effects model. The second meta-analysis for mean arterial pressure followed a fixed effects model, and data were derived from 3 articles. No statistical difference was found in mean arterial pressure values between the groups [MD = 0.99; 95% CI, -2.24, 4.22; I2 = 0%; P = 0.55]. Data from 4 articles (all RCTs) were used for the analysis of cerebral perfusion pressure and followed a random effects model. Ketamine administration was comparable with opioids in the maintenance of cerebral perfusion pressure. [MD = -1.07; 95% CI, -7.95, 5.8; I2 = 83%; P = 0.76]. Thus, in none of the analyses performed by the authors was a significant difference in outcome detected.

To the author's knowledge, Wang et al. was the first study to perform meta-analyses on the topic. However, the two meta-analyses presented in their systematic review regarding intracranial pressure and cerebral perfusion pressure, had high heterogeneity at I = 85% and I = 83%, respectively. Although this may still yield useful results, it reflects a similar level of uncertainty and heterogeneity in the evidence. Until large, high-quality, pragmatic randomised controlled trials are performed to strengthen the evidence base and reduce the conflicting study results emanating from smaller, lower-quality studies, these meta-analyses will be of limited use to inform practice.

Table 3.3 provides a summary of an excluded RCT on ketamine which may provide some insights into the effectiveness and safety of ketamine for induction of traumatic brain injury patients. Jabre et al.[49] was the largest RCT found by the authors, with 655 critically ill patients who needed sedation for emergency intubation which were prospectively enrolled from 12 emergency medical services or

emergency departments and 65 intensive care units in France. Patients were randomly assigned by a computerised random-number generator list to receive 0.3 mg/kg of etomidate (n=328) or 2 mg/kg of ketamine (n=327) for intubation.

Although the authors included a subgroup for trauma patients, they did not specify which patients within that subgroup were TBI patients. Thus, we cannot extract data regarding our population of interest. However, the authors found that the mean maximum Sequential Organ Failure Assessment (SOFA) score between the two groups did not differ significantly (10.3 [SD 3.7] for etomidate vs 9.6 [SD 3.9] for ketamine; mean difference 0.7 [95% CI 0.0–1.4], p=0.056). Intubation conditions did not differ significantly between the two groups (median intubation difficulty score 1 [IQR 0–3] in both groups; p=0.70). The percentage of patients with adrenal insufficiency was significantly higher in the etomidate group than in the ketamine group (OR 6.7, 3.5–12.7, 95% Cl). No serious adverse events with either study drug were recorded.

The authors stated that ketamine is a safe and clinically valuable alternative to etomidate for endotracheal intubation in critically ill patients. Although TBI patients were included in their study, no adverse events or increases in mortality were observed in the ketamine group. This shows that ketamine likely has no negative effects for this specific subset of patients, or the rate of adverse events would have been higher in the ketamine group. Thus, ketamine is safe to use in critically ill patients, including patients who have suffered trauma. However, the question of whether ketamine may be harmful to TBI patients is still uncertain as it has not been specifically addressed in this RCT.

Given that only one RCT found in the tier 3 searches was appreciably close to this review's research question, the same trend found in tier 1 and 2 has continued through tier 3. Ongoing research, as in the case of Driver et al. [41] (if the authors include a subgroup for traumatic brain injury patients) have the potential to answer the research question in future. However, at this time there is a significant lack of empirical evidence and considerable knowledge gaps regarding the effectiveness and safety of ketamine in TBI patients in the prehospital and emergency department settings. Although cohort and other study designs can provide some evidence at less scientifically robust levels, RCTs remain the desired study design to provide an evidence base regarding the research question.

The prehospital and emergency centre settings share many commonalities in the context of this review as adults with acute TBI emergencies would present to both settings in need of advanced airway management. However, the research bases for these two settings are significantly different.

Prehospital medicine is a 'relatively new' concept in terms of medicine as a whole, and as such does not have such an established evidence base when compared to the emergency centre. However, growing interest in improving prehospital care has significantly increased the research output in the prehospital field and it has become a fast-growing industry.

Tiered approaches to searching and identification of studies for inclusion are a relatively novel review design. The tiered design offers significant benefits to both clinical policymakers and practitioners in healthcare as it is effective in answering research questions that require rapid responses for the healthcare industry. It is not limited to searching for primary evidence only, but includes study designs such as systematic reviews and clinical practice guidelines to inform the research question. It is possible, for the reviewer to then adopt, adapt or contextualise a clinically relevant clinical practice guideline's recommendations to answer their research question, as opposed to searching for primary evidence, synthesizing that evidence and formulating their own recommendations to inform practice. In terms of systematic searching, tiered approaches search for a wider variety of study designs, depending on the different study design/s searched for in each tier of inclusion. This adds to the thoroughness of a review, especially in cases where clinical questions require an answer within a limited timeframe and budget. Lower- and middle income countries can benefit from tiered approaches as recommendations made in CPGs and SRs from high-income countries can be adopted, adapted or contextualised to their unique circumstances.

Limitations

The study design was limited in search depth as articles published in languages other than English were excluded. Due to time and resource limitations, this was unfortunately not a feasible undertaking. Some articles published in other languages, where the abstract had been translated to English were found in the searches. However, these articles were not relevant to the research question. Also, grey literature was not included in this review.

Although this review followed a tiered design which covered a wider variety of study designs sought for inclusion (CPGs, SRs and RCTs) as compared to a traditional systematic review where only RCTs are sought, searches were not continued for other study designs which may have been able to answer the research question, e.g. cohort studies. However, extending the searches past RCT level would significantly increase the resource and time requirements, and was not possible within the current scope.

Conclusions

Implication for Practice

We found no clinical practice guidelines, systematic reviews or randomised controlled trials which met our inclusion criteria in this review. The effectiveness and safety of ketamine for induction to facilitate intubation in adult TBI patients in the South African pre-hospital setting remains unclear. Due to a lack of empirical evidence, practitioners must be cautious and ensure that the benefit from its use outweighs the potential harm for a particular patient.

Implication for Research

Large, pragmatic randomised controlled trials are needed to provide an evidence base for ketamine's safety and effectiveness. Ideally, these studies should be performed on TBI patients in the prehospital or emergency department settings, and should include both doctors and paramedics as the treating personnel.

Ketamine as a bolus for induction to facilitate intubation in adult and/or paediatric patients should be compared to a reasonable induction agent available to the treating practitioners, such as etomidate, midazolam or propofol. As all-cause mortality would be a useful primary outcome; secondary outcomes such as intracranial pressure, cerebral perfusion pressure and mean arterial pressure could be helpful to improve our understanding of ketamine's effectiveness and safety in TBI patients.

Updates

This review will be updated in two years and any new information regarding the research question will be provided in an update on this dissertation.

Acknowledgements

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References to Excluded Studies

Aroni F, Iacovidou N, Dontas I, Pourzitaki C, Xanthos T. Pharmacological Aspects and Potential New Clinical Applications of Ketamine: Reevaluation of an Old Drug. The Journal of Clinical Pharmacology. 2009;49(8):957-64.

Abdennour L. & Puybasset L. Sedation and analgesia for the brain-injured patient. Ann Fr Anesth Reanim 2008; 27(7-8):596-603.

Abdusoglu M.N., et al. The Effects of a Subhypnotic Dose of Ketamine on Neuromuscular Block Characteristics of Rocuronium and Intubation Quality. Turkiye Klinikleri Journal of Medical Sciences 2012; 32(2):399-406.

Albanese J., Garnier F., Bourgoin A., Leone M. The Agents Used for Sedation in Neuroprotective Care Unit. Ann Fr Anesth Reanim 2004; 23(5):528-34.

Armstrong B., Reid C., Heath P., Simpson H., Kitching J., Nicholas J., Chan L., Taylor J. & Rush H. Rapid Sequence Induction Anaesthesia: A Guide for Nurses in the Emergency Department. International Emergency Nursing 2009; 17:161-168.

Bedell E, Prough DS. Anesthetic management of traumatic brain injury. Anesthesiology Clinics of North America. 2002;20(2):417-39.

Bourgoin A., Albanese J., Wereszczynski N., Charbit M., Vialet R., Martin C. Safety of Sedation with Ketamine in Severe Head Injury Patients: Comparison with Sufentanil. Crit Care Med 2003; 31(3):711-717.

Canadian Agency for Drugs and Technology in Health. Ketamine for Adult Patients who have Suffered Painful and Traumatic Injuries: A Review of Clinical Effectiveness Cost-Effectiveness, Safety and Guidelines. CADTH 2014.

Chang LC, Raty SR, Ortiz J, Bailard NS, Mathew SJ. The Emerging Use of Ketamine for Anesthesia and Sedation in Traumatic Brain Injuries. CNS neuroscience & therapeutics. 2013;19(6):390-5.

Cohen L, et al. The Effect of Ketamine on Intracranial and Cerebral Perfusion Pressure and Health Outcomes: A Systematic Review. Annals of Emergency Medicine 2015; 65(1):43-51.

Cormio M, Robertson CS, Narayan RK. Secondary insults to the injured brain. Journal of Clinical Neuroscience. 1997;4(2):132-48.

Craven R. Ketamine. Anaesthesia. 2007;62:48-53.

Dash HH. Prehospital Care of Head Injured Patients. Neurology India 2008; 56(4): 415-419.

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(2):154-7.

Freund Y., Jabre P., Mourad J., Lapostolle F., Reuter PG., Woimant M., Javaud N., Adnet F. Relative Adrenal Insufficiency in Critically Ill Patient after Rapid Sequence Intubation: KETASED ancillary study. Journal of Critical Care 2014; 29(3):386-389.

Green SM., Roback MG., Kennedy RM., Krauss B. Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update. Annals of Emergency Medicine 2011; 57(5):449-461.

Gunning M., Perkins Z., Quinn T. Trench Entrapment: is Ketamine Safe to use for Sedation in Head Injury. Emerg Med J 2007;24(11):794-5.

Harris T., Davenport R., Hurst T. & Jones J. Improving Outcome in Severe Trauma: Trauma Systems and Initial Management - Intubation, Ventilation and Resuscitation. Postgrad Med J 2012; 88:588-594.

Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? Anesth Analg. 2005;101(2):524-34, table of contents.

Hughes S. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 3: is ketamine a viable induction agent for the trauma patient with potential brain injury. Emergency medicine journal : EMJ. 2011;28(12):1076-7.

Hulme J. Resuscitation of Patients after Traumatic Brain Injury. Trauma 2008; 10:55-63.

Jabre P., et al. Etomidate Versus Ketamine for Rapid Sequence Intubation in Acutely Ill Patients: a Multicentre Randomised Controlled Trial. Lancet 2009; 374(9686):293-300.

Jensen AG., Callesen T., Hagemo JS., Hreinsson K., Lund V. & Nordmark J. Scandinavian Clinical Practice Guidelines on General Anaesthesia for Emergency Situations. Acta Anaesthesiol Scand 2010; 54:922-950.

Lockey DJ., Crewdson K. & Lossius HM. Pre-Hospital Anaesthesia: The Same but Different. British Journal of Anaesthesia 2014; 113(2): 211-219.

Martin J., Franck M., Fischer M. & Spies C. Sedation and Analgesia in German Intensive Care Units: How is it done in reality? Results of a Patient-based Survey of Analgesia and Sedation.

Matthes G., et al. Emergency Anesthesia, Airway Management and Ventilation in Major Trauma. Background and Key Messages of the Interdisciplinary S3 Guidelines for Major Trauma Patients. Unfallchirurg 2012; 115(3): 251-264.

Mayglothling J., Duane TM., Gibbs M., McCunn M., Legome E., Eastman AL., Whelan J & Shah KH. Emergency Tracheal Intubation Immediately Following Traumatic Injury: An Eastern Association for the Surgery of Trauma Practice Management Guideline. Trauma Acute Care Surg 2012;

73(5):S333-S340.

McDermott P. & Sebastian J. Should Ketamine be used as an Induction Agent in Traumatic Brain Injury? British Journal of Hospital Medicine 2013; 74(9): 538.

McIntosh TK, Juhler M, Wieloch T. Novel pharmacologic strategies in the treatment of experimental traumatic brain injury: 1998. Journal of Neurotrauma. 1998;15(10):731-69.

McIntosh TK, Smith DH, Garde E. Therapeutic approaches for the prevention of secondary brain injury. European Journal of Anaesthesiology. 1996;13(3):291-309.

Morris C, Perris A, Klein J, Mahoney P. Anaesthesia in haemodynamically compromised emergency patients: does ketamine represent the best choice of induction agent? Anaesthesia. 2009;64(5):532-9.

Paal P., Herff H., Mitterlechner T., Von Goedecke A., Brugger H., Lindner KH. & Wenzel V. Anaesthesia in Prehospital Emergencies and in the Emergency Room. Resuscitation 2010; 81:148-154.

Pasternak JJ. & Lanier WL. Neuroanaesthesiology Review. J Neurosurg Anesthesiol 2008; 20:78-104.

Roberts DJ, Hall RI, Kramer AH, Robertson HL, Gallagher CN, Zygun DA. Sedation for critically ill adults with severe traumatic brain injury: a systematic review of randomized controlled trials. Crit Care Med. 2011;39(12):2743-51.

Royal Flying Doctor Service. Clinical Guidelines (Version 5.0). 2008.

Scarponcini TR., Edwards CJ., Rudis M., Jasiak KD. & Hays DP. The Role of the Emergency Pharmacist in Trauma Resuscitation. Journal of Pharmacy Practice 2011; 24(2):146-159.

Seder DB. & Riker RR. Emergency Neurological Life Support: Airway, Ventilation and Sedation. Neurocrit Care 2012; 17:S4-S20.

Sehdev RS, Symmons DA, Kindl K. Ketamine for rapid sequence induction in patients with head injury in the emergency department. Emergency medicine Australasia: EMA. 2006;18(1):37-44.

Sih K, Campbell SG, Tallon JM, Magee K, Zed PJ. Ketamine in adult emergency medicine: controversies and recent advances. The Annals of pharmacotherapy. 2011;45(12):1525-34.

Tobin JM., Gabinsky A., McCunn M., Pittet JF., Smith CE., Murray MJ. & Varon AJ. A Checklist for Trauma and Emergency Anaesthesia. International Anesthesia Research Society 2013; 117(5): 1178-1185.

Urwin SC, Menon DK. Comparative tolerability of sedative agents in head-injured adults. Drug safety. 2004;27(2):107-33.

Vutskits L. General anesthetics in brain injury: friends or foes? Current pharmaceutical design. 2014;20(26):4203-10.

Wang X, Ding X, Tong Y, Zong J, Zhao X, Ren H, Li Q. Ketamine Does Not Increase Intracranial Pressure Compared with Opioids: Meta-Analysis of Randomised Controlled Trials. J Anesth 2014; 28(6):821-7.

Wenzel V. & Lindner KH. Best Pharmacological Practice in Prehospital Intubation. The Lancet 2009; 374: 267-268.

Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on ICP in traumatic brain injury. Neurocrit Care. 2014;21(1):163-73.

References to Included Studies

No included studies found

Tables

Characteristics of Excluded Studies

Table 1.1: Tier 1 table of excluded studies

Study	Reason for Exclusion
Armstrong 2009	Literature review which reports on a checklist designed specifically for nurses (or an assistant) in the process of rapid sequence intubation.
CADTH 2014	Literature review which reports on Ketamine being used as an analgesic agent and not an induction agent.
Dash 2008	Literature review which details the different components of prehospital care in head injury patients.
Green 2011	CPG regarding Ketamine dissociative sedation in the emergency department. Unclear methodology, reported in an end-user format. Unclear link between recommendations and evidence. Unable to identify clear CPG recommendations. Specifically deals with ketamine dissociative sedation in the ED, but does not report on the study population of interest (TBI patients).
Harris 2015	Literature review of endotracheal intubation in general. No

	recommendations were made regarding Ketamine which could be extracted.
Hulme 2008	Literature Review regarding the resuscitation of patients after traumatic brain injury, pertaining to airway management, intracranial pressure, prognostic factors and prevention of secondary brain injury. No recommendations about Ketamine which pertains to the research question were made.
Jensen 2010	CPG regarding general anaesthesia of emergency patients. Recommendations regarding pre-surgical management, induction of anaesthesia and airway management considerations are made.
Lockey 2013	Literature review regarding controversies and challenges in the pre-hospital environment.
Martin 2006	Descriptive study on patient-based outcomes of sedation and analgesia in German intensive care units.
Mayglothling 2012	CPG regarding intubation of emergency trauma patients. However, there are no outcomes/ recommendations to extract regarding induction agents (including Ketamine) used in RSI.
Paal 2009	Literature review on the use of anaesthetic agents in prehospital care. No recommendations were made regarding ketamine use in TBI patients.
Pasternak 2007	Literature review regarding anaesthesiology practices and perioperative care of neurosurgery patients.
RDFS 2008	CPG on the recommendations of emergency care from the Royal Doctor Flying Service. Not relevant to our research question.
Scarponcini 2011	Literature Review regarding the incorporation of an emergency pharmacist in trauma resuscitation.
Seder 2012	Resembles an end-user document, which outlines the process of deciding to intubate, sedation and intubation. Does mention Ketamine, but makes no recommendations regarding its use.
Tobin 2013	Literature review regarding Ketamine use in head-injured patients. No recommendations were made.
Wenzel 2009	Commentary on an RCT published by Jabre et al 2009, which in turn compared mean Sequential Organ Failure Assessment (SOFA) score after Ketamine/Etomidate Administration

Table 1.2: Tier 2 table of excluded studies

Study	Reason for Exclusion
Aroni et al. 2009	Literature review of the pharmacological aspects of Ketamine with regards to its effects on the central nervous system, haemodynamic effects and use as pain management agent.
Bedell 2002	Literatures review which reports on the interventions which may be likely to improve survival after a significant TBI, such as prevention of hypotension, hypoxia and hypoglycaemia.
Chang et al. 2013	Literature review regarding neuroprotective effects of ketamine in traumatic brain injured patients. Not applicable to study research question.
Cohen et al. 2015	Systematic review of Ketamine use in ICU and operating room (OR) patients, and although it reports data which is relevant to our research question, it only reports these outcomes for ICU and OR patients and not the population of interest for our review.
Cormio 1997	Literature review regarding the pathological processes involved in traumatic brain injuries, specifically regarding secondary brain injury.
Craven 2007	End-user document for clinicians to familiarise themselves with Ketamine, its use and its effects. It includes practical examples and scenarios to stimulate critical thinking regarding the use of Ketamine
Dash 2008	Literature review reporting on the challenges faced to achieve prehospital emergency medical care in India. Although Ketamine is mentioned, it is not done so in the context which would make it relevant to our review.
Filanovsky et al. 2010	Literature review regarding ICP levels after ketamine was administered in ICU patients. A search strategy was reported, however it followed a non-systematic method.
Himmelseher 2005	Systematic review of ketamine use and cerebral effects in neurosurgical patients.
Hughes 2011	Not a systematic review, but what was referred to by the study author as a “short-cut review”, regarding the use of ketamine as an induction agent for intubation in adults with traumatic brain injury. Although the review matches our research question closely, they did not perform a review of RCTs, but based their results on a case report and a study which does not apply to our research question. Unclear methods.

McIntosh 1996	Literature review regarding pharmacological manipulation of key neurotransmitters in the brain that can attenuate neuronal damage. Not relevant to our research question.
McIntosh 1998	This article is related to the one above, which was previously published by the same author. Not Relevant to our research question.
Morris et al. 2009	Literature review regarding induction with ketamine in hemodynamically unstable patients and the effect it has on the patient's hemodynamics. Not the population of interest.
Roberts 2011	Systematic review of critically ill ICU patients with severe head injury who were sedated using ketamine, propofol, etomidate and other sedatives. Not the review's population of interest.
Sehdev 2006	Literature Review of Ketamine use in head injured patients in the ED to facilitate intubation. This study did not report on any RCT, which meant its exclusion.
Sih 2011	Systematic review where the outcomes were narratively reported. Although it assesses Ketamine use in the ED to facilitate endotracheal intubation, none of the included studies reported on head injury patients.
Urwin 2004	Literature review with methods not clearly stated. Describes the effects of multiple induction agents in head injury patients. Does not report a search strategy, appraisal method/s or inclusion/exclusion criteria.
Vutskits 2014	Not relevant to our research question. Primarily deals with medications used for neuroprotection in in head-injured patients.
Wang et al. 2014	Systematic review, which much like Cohen et al 2015, reports on outcomes which are relevant to our research question. However, as above, it only reports these outcomes for ICU, paediatric and patients which do not fall within the populations of interest for the review.
Zeiler 2014	Systematic review. However, it only reports on patients in the ICU and not the population of interest for the Review

Table 1.3: Tier 3 table of excluded studies

Abdennour 2008	Article Published in French
Abdusoglu 2012	Does include ketamine as intervention, however ketamine as

	given as an analgesic locally to prevent pain from propofol or rocuronium injections. Thus, does not apply to our PICO.
Albanese 2004	Article Published in French
Bourgoin 2003	Ketamine not given as an induction agent or as a bolus. Article does not deal with intubation, but rather with Ketamine given as a bolus in ICU to determine its effects on ICP.
Freund 2014	Does include Ketamine in the study, but only reports on outcomes related to Etomidate and relative adrenal insufficiency.
Gunning 2007	Case Report of a patient involved in a trench entrapment - not an RCT.
Jabre 2009	Study very close to our review's inclusion criteria. Acutely ill patients as population, which includes trauma patients. However, does not include head injured patients as a subgroup in the trauma category, i.e. cannot extract data relevant to our PICO.
Matthes 2012	Article is published in German
McDermott 2013	Literature review regarding ketamine use as an induction agent in head-injured patients. Methods unclear. No delineation given of outcomes, setting, comparators or how the intervention was applied (doses, time over which dose was given and clinical setting)

Table 2.1: Table of Clinical Practice Guidelines (Tier 1) on Ketamine

Reference	**Green, et al** [52]
Purpose/Scope	To describe the best available evidence and perspectives about optimal dissociative sedation practice in the Emergency Department
Guideline Questions	None specified
Methods	Assembled a committee of 4 senior ketamine researchers. **Searched** ● MEDLINE: ● January 2003 to November 2010, using the single search term "Ketamine". ● Tables of contents of the leading emergency medicine and anaesthesiology journals during the same period. ● Reference lists of all identified articles for additional relevant articles. **Study Inclusion and Grading** Study inclusion/exclusion was debated by e-mail and during a group meeting on September 12, 2010. They graded the availability and strength of scientific evidence from the medical

	literature, using descriptive terms adapted from the American Society of Anaesthesiologists
Summary Recommendations	As per table 1.1, Tier 1 table of excluded studies, there is an unclear link between recommendations and the evidence. The authors are unable to identify clear recommendations from the CPG.
Comments	This CPG resembles and end-user document, where the focus is not specific recommendations based on the literature and evidence, but rather to produce a guideline for the procedure in which to identify the need for ketamine dissociative sedation, indications, contraindications, administration and techniques/ manners in which to reduce the incidence of adverse effects. Therefore, it is reasonable to consider this a clinical protocol and not a true CPG, as recommendations are not clearly stated. It is, however, a very informative document and covers the topic in sufficient depth to be useful as a protocol for healthcare practitioners who are not well versed in Ketamine use and its effects, or unsure of its application and role in their clinical setting.

Reference	**Mayglothling, et al** [53]
Purpose/Scope	The goals of the work group were to develop evidence-based guidelines to (1) characterize patients in need of ETI and (2) delineate the most appropriate procedure for patients undergoing ETI.
Guideline Questions	1. Are the 2002 guidelines still valid, and is there any new evidence to change the level of the previous recommendations? 2. Is direct laryngoscopy (DL) still the preferred method for ETI in trauma? 3. What is the role of newly introduced airway adjuncts, such as blind insertion supraglottic devices and video laryngoscopy? 4. Are there pharmacologic agents used for intubation that should be recommended for or against in the setting of acute injury? 5. What is the role of prehospital ETI?
Methods	**<u>Searches</u>** ● MEDLINE - Citations published between January 2001 and December 2011. This included a combination of MESH headings and title words. ● In addition to the MEDLINE search, bibliography of reviews, letters to the editor, and meta-analyses were used to identify other relevant patient investigation articles. If an article investigated trauma and medical patients, the article was included if the trauma patient cohort was at least 50% or if the study included a subgroup analysis on the specific trauma population. ● Articles and recommendations were classified as described in the EAST primer on using evidence-based outcome measures to develop practice management guidelines.
Summary Recommendations	● In terms of airway management, it is recommended that a careful airway assessment be conducted before efforts to secure the airway are initiated. (Level 2) Proper preparation in terms of airway devices, techniques, medications and bail-out options should be made for a suspected difficult airway. (Level 2) ● In terms of indications of endotracheal intubation (ETI), it is indicated for trauma patients with airway obstruction, hypoventilation, persistent hypoxaemia, GCS ≤ 8, severe haemorrhagic shock and cardiac arrest. ETI is also indicated for patients with smoke inhalation and airway obstruction, GCS ≤ 8, >40% burns, prolonged time to definitive care and impending airway obstruction (Level 1) ● ETI is also indicated for trauma patients with facial or neck injury with potential airway obstruction, GCS ≤ 9, persistent combativeness despite pharmacological agent use, respiratory distress, preoperative management, and cervical spine injuries with respiratory compromise. (Level 3)

	● In terms of procedural options, ETI by direct laryngoscopy is the preferred method for trauma patients. Rapid sequence intubation (RSI) should be used unless there are specific contraindications to its use. There are no recommendations regarding the use of specific induction agents used for RSI in trauma. Succinylcholine is the recommended agent of choice for neuromuscular blockade, in the absence of any contraindications to its use. ● For safe and effective ETI, experienced personnel should be available, pulse-oximetry be monitored, cervical neutrality maintained, confirmation of tube placement be done by both auscultation and end-tidal CO2 monitoring and continuous end-tidal CO2 monitoring be maintained continuously. ● Cricothyroidostomy is indicated if direct laryngoscopy and alternative methods fail. Airway rescue devices such as blind insertion devices and intubation adjuncts should be used when direct laryngoscopy fails. (Level 2) ● Video laryngoscopy may offer significant advantages over Direct laryngoscopy. ● Superior views of the glottis, higher intubation success rates for patient with confirmed difficult airway, and higher intubation success rates by inexperienced airway providers.
Comments	This particular CPG made no recommendations regarding the agents used for induction in intubation or rapid sequence intubation. Thus, it was excluded from the study. However, it does make recommendations regarding intubation in head injured patients, and specifically regarding how to prevent adverse events before, during and after intubation of these patients. It would be helpful to both inexperienced and experienced provides to improve their management of the airway in traumatic brain injury patients.

Reference	**Jensen, et al** [50]
Purpose/Scope	The aim of this CPG was to find the evidence and latest scientific information for their current anaesthetic management of emergency patients, and thereby to provide anaesthesiologists in the Nordic countries with a mutual understanding and a standardised protocol to anaesthetize these patients
Guideline Questions	None specified
Methods	**Searches** ● PubMed, inclusive of Mesh, and the Cochrane Library from August 1961 to May 2009 ● Cross references from relevant studies has been used. ● Grading of evidence and grading of recommendations were performed according to a system first used by Bell et al.[54] According to this system, evidence is graded from A to E, where recommendation grade A indicates a recommendation based on the best evidence. ● The individual chapters were written in drafts, and after initial discussions via mail, a consensus meeting was held. Evidence was assessed and grading of recommendations was decided. Consensus opinion was used in the many topics where high-grade evidence was unavailable. ● The specific grading of evidence and grading of recommendation can be found in the individual chapters, where a draft with recommendations was presented at the 30th Congress of SSAI, June 2009. ● Comments from this presentation were incorporated into the next draft, and this draft was presented for comments and critique on the SSAI website from August until November 2009.
Summary Recommendations	**Pre-operatively** ● Anaesthesia for emergency patients should be given by, or under very close supervision by, an experienced anaesthesiologist. Haemodynamic and airway-related complications should be anticipated. Alternative plans and adequate equipment for

	dealing with complications must be ready. ● In patients with an increased risk of aspiration, precautions to avoid regurgitation must be taken. ● Unless the patient has an increased risk of aspiration, patients scheduled for emergency surgery can be considered fasting. ● Pre-operative gastric emptying with an orogastric or a nasogastric tube is rarely indicated. **Pre-oxygenation and cricoid pressure** ● Pre-oxygenation is initiated by explaining the procedure to the patient. ● Avoid a leak between the patient's face and the oxygen mask. ● Either tidal volume breathing for 3 min or eight deep breaths over 60 s with an oxygen flow of at least 10 l/min should be used. ● Non-invasive positive pressure ventilation or the application of positive end-expiratory pressure can be considered in morbidly obese or critically ill hypoxic patients. ● Pre-oxygenation in obese patients should be performed in the head-up position; otherwise, there is no advantage of one placement over the other. ● The use of cricoid pressure is not considered mandatory, but can be used on individual judgement. ● If used, the cricoid pressure must be used correctly, and the pressure should be released if ventilation or laryngoscopy and intubation are difficult. ● Cricoid pressure should also be released before inserting the Laryngeal Mask Airway should initial attempts at tracheal intubation prove Unsuccessful. **Drugs** ● The hypnotic drug has a minor influence on intubation conditions, and should be chosen on other grounds. ● Thiopentone seems to be a better choice than propofol to avoid hypotension following induction. ● On the other hand, propofol is a better choice than thiopentone to avoid a cardiovascular stress response in patients with ischaemic cardiac disease. ● Ketamine should be considered for hypovolaemic patients (hypovolaemic shock or pre-shock) or for cardiovascular unstable patients when there is no time or possibility of pre-operative optimization. ● An opioid can be used to reduce the stress response following intubation. ● A neuromuscular blocking agent is used to optimize intubation conditions. ● For optimal intubation conditions, succinylcholine 1–1.5 mg/kg is preferred over other neuromuscular blocking drugs. ● Where contraindications to succinylcholine exist, rocuronium 0.9–1.2 mg/kg is an adequate alternative. **Anaesthesia outside the operation room** ● Rapid sequence intubation is considered the safest method. ● Awake intubation can be performed in selected cases. ● For induction of anaesthesia, all available induction agents can be used. **End of anaesthesia** Take precautions also at the end of anaesthesia to avoid haemodynamic and airway-related complications as well as regurgitation.
Comments	Of the three CPGs which were discussed here, this CPG reports their methods and results significantly better than the above two. However, these recommendations are made

	without a clear clinical setting identified. It is a very informative document regarding the current practices in the Scandinavian anaesthesia setting. However, as the 'current Scandinavian anaesthetic management of emergency patients' is not specified in the document, nor the evidence and literature as to why that is the norm, it is impossible to apply the recommendations to any other clinical setting than Scandinavia. However, it does provide some insights into anaesthesia of emergency patients, and emphasises the importance of having standardised practice regimes within a healthcare system/speciality.

Table 2.2: Table of Systematic Reviews (Tier 2) on Ketamine

Reference	**Cohen, et al. 2015** [51]
Research Question	Does ketamine raise intracranial pressure or worsen neurologic outcomes?
Intervention/Comparison description	Ketamine used as an infusion or bolus dose compared to other sedative agents in patients who had previously been intubated or who were being intubated at data collection.
Results	**Intracranial pressure and cerebral perfusion pressure** Three randomized trials and 5 prospective controlled trials. Studies examined the relationship between ketamine and comparator induction agents with respect to intracranial and cerebral perfusion pressures, and reported data on 168 patients. These studies found no differences in mean daily intracranial or cerebral perfusion pressures. **Neurologic outcomes** Four of the 5 included randomized trials reported data on neurologic outcomes reporting data on 824 patients. Studies used different neurologic outcome scales and collected data at different points, precluding any pooling of data. However, within each individual included study, none of them reported statistically significant difference between the intervention and control groups (based on the neurological outcome scale they used). **ICU length of stay** Two randomized studies reported ICU length of stay as a study outcome (n¼145). Neither study found a difference in length of stay. **Mortality** Two randomised trials reported mortality data on 680 patients. Neither study found a difference in Mortality.
Comments	This study had very similar outcome measures to this review. However, all the studies they included in their systematic review were not the population of interest for this review. Thus, it could not be included. However, this study provides a great deal of insight into the safety and effectiveness of Ketamine used to facilitate intubation in other patient populations, such as surgical or ICU patients. In none of the outcome measures, intracranial pressure and cerebral perfusion pressure, neurologic outcomes, ICU length of stay and mortality, did they report in difference in the outcomes between ketamine and comparison agents. Without empirical evidence for the pre-hospital or emergency department settings, ketamine effectiveness and safety in these settings cannot be clearly stated. However, it is promising to note that, at least in surgical and ICU patients, these outcomes have shown no difference. This article helps to highlight one of the current gaps in knowledge regarding Ketamine, as it not yet clear what its effectiveness and safety in the population of interest is.

Reference	**Wang et al. 2014** [55]

Research Question	What are the effects of ketamine on cerebral hemodynamics in comparison with opioids in patients with or without neurological injury?
Intervention/Comparison description	RCTs conducted in humans of cerebral hemodynamics comparing ketamine with opioids, regardless of whether the subjects were head injured, ventilated, underwent surgery, or received additional medications. The study analysed the ICP levels after administration of ketamine or opioids. The dose, timing, and other details of anaesthesia drugs were not limitations.
Results	**ICP** Meta-analysis showed that ketamine led to the same ICP levels as did opioids, which was one of the common agents for sedation (mainly sufentanil and fentanyl) (MD = 1.94; 95 % CI, -2.35, 6.23; I2 = 85 %; P = 0.38) **MAP** Data were derived from three articles for the analysis of MAP. No statistical significance was found in MAP values between the groups (MD = 0.99; 95 % CI, -2.24, 4.22; I2 = 0 %; P = 0.55). **CPP** Data from four articles were used for the analysis of CPP. Ketamine administration was comparable with opioids in the maintenance of CPP (MD = -1.07; 95 % CI, -7.95, 5.8; I2 = 83 %; P = 0.76)
Comments	A random effects meta-analysis was conducted on intensive care patients comparing ketamine to opioids for ICP for MAP and CCP, a fixed effects meta-analysis was conducted on intensive care patients comparing ketamine to opioids. Although our review did not use cerebral heamodynamics following ketamine administration as an outcome, knowing the effects of Ketamine on ICP, MAP and CPP could assist greatly with describing Ketamine's effects on the body and brain.

Table 2.3: Table of Randomised Controlled Trials (Tier 3) on Ketamine

Reference	**Jabre et al. 2009** [56]
Research Question	What is the early and 28-day mortality of a single dose ketamine compared to etomidate, for emergency endotracheal intubation of critically ill patients?
Intervention/Comparison description	Patients were randomly assigned in a 1:1 ratio to either etomidate (Lipuro, B Braun Medical, Boulogne, France) administered as a 0·3 mg/kg intravenous bolus, or to ketamine (Ketalar, Panpharma, Fougères, France) administered as a 2 mg/kg intravenous bolus.
Results	***See Reference***
Comments	To date, this is the largest RCT the authors have found which compares ketamine to another induction agent (etomidate) currently being used in the South African pre-hospital setting. Although this study included a subgroup of trauma patients, the authors did not specify which subset of the trauma patients had with traumatic brain injuries. This meant the exclusion of the article from the review. However, this RCT is very informative as it compares ketamine and etomidate in a generalised population group (critically ill patients), improving its external validity to more patient populations than a study with a very specific study population.

Appendices

Appendix 1: Search Strategies

Appendix 1.1: Clinical Practice Guidelines (Tier 1)

1. Ketamine OR Ketalar OR Brevinase AND Head Injur* OR Brain Injur* OR traumatic brain injur* OR Head trauma

Adapted according to search results as CPG databases are less refined

Appendix 1.2: Systematic Reviews (Tier 2)

1. **Cochrane Library**

   ((((((("Ketamine"[Mesh]) OR ketamine[Title/Abstract])) OR Brevinase[Title/Abstract]) OR Ketalar[Title/Abstract])) AND

   ((((((("Craniocerebral Trauma"[Mesh] OR "Head Injuries, Penetrating"[Mesh] OR "Head Injuries, Closed"[Mesh])) OR head injur*[Title/Abstract]) OR head trauma[Title/Abstract]) OR traumatic brain injur*[Title/Abstract]) OR "Brain Injuries"[Mesh])

Appendix 1.3:Randomised Controlled Trials (Tier 3)

1. **Pubmed**

   ((((((("Ketamine"[Mesh]) OR ketamine[Title/Abstract])) OR Brevinase[Title/Abstract]) OR Ketalar[Title/Abstract])) AND ((((((("Craniocerebral Trauma"[Mesh] OR "Head Injuries, Penetrating"[Mesh] OR "Head Injuries, Closed"[Mesh])) OR head injur*[Title/Abstract]) OR head trauma[Title/Abstract]) OR traumatic brain injur*[Title/Abstract]) OR "Brain Injuries"[Mesh])

2. **Scopus and Cochrane CENTRAL Library**

   ketamine OR brevinase OR ketalar AND craniocerebral trauma OR head injur* OR head trauma OR traumatic brain injur* OR brain injur*

Appendix 2: Aggregate Scores and Graphical Representation of Quality of Reporting of Clinical Practice Guidelines (AGREE II)

Study Name	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Overall CPG Assessment Score
Green, et al. 2011	25%	11.1%	18.8%	19.4%	10.4%	20.8%	2 out of 7
Mayglothling, et al. 2012	33.3%	5.5%	36.5%	34.8%	0%	50%	2 out of 7
Jensen, et al. 2010	30.6%	25%	47.9%	63.9%	13%	0%	3 out of 7

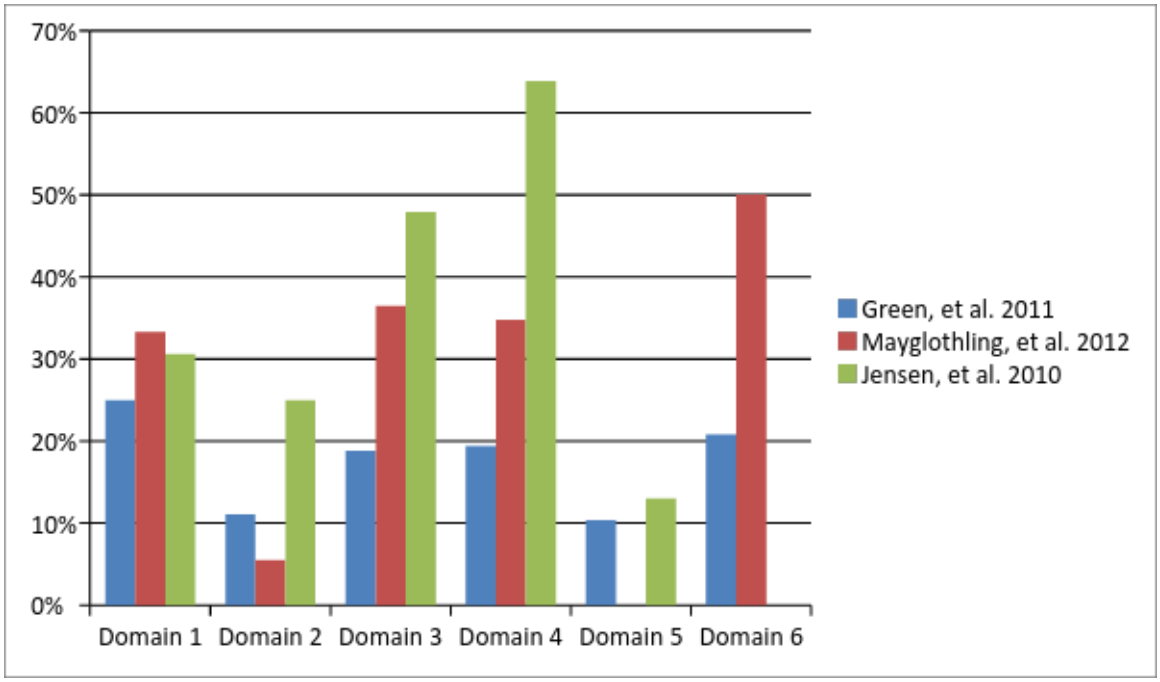

Figure 4: Graph of Aggregate Scores Obtained by 3 CPGs for AGREE II

References

1. History of Ketamine [Internet]. [cited 2016 Mar 30]. Available from: http://ketamine.com/history-of-ketamine/

2. Rogers K. Ketamine. In: Encyclopedia Brittanica. 2014.

3. Jansen KL. A Review of the Non-medical use of Ketamine: Use, Users and Consequences. J Psychoactive Drugs. 2000;32:419–33.

4. World Health Organisation. Critical Review on Ketamine. In: 34th ECDD. World Health Organisation; 2006.

5. Drummond GB. Comparison of Sedation with Midazolam and Ketamine: Effects on Airway Muscle Activity. Br J Anaesth. 1996;76:663–7.

6. Pai A. Ketamine. Contin Educ Anaesth Crit Care Pain. 2007;7(2):59–63.

7. Burns SM. Delirium During Emergence From Anaesthesia: A Case Study. Crit Care Nurse. 2003;23(1):66–9.

8. Grace RF. The Effect of Variable-Dose Diazepam on Dreaming and Emergence Phenomena in 400 Cases of Ketamine-Fentanyl Anaesthesia. Anaesthesia. 2003;58(9):904.

9. Lamb WV, Jones EW. Veterinary Anaesthesia. 1973;680.

10. Gibbs JM. The Effect of Intravenous Ketamine on Cerebrospinal Fluid Pressure. Br J Anaesth. 1972;44(12):1298–302.

11. Evans J, Rosen M, Weeks RD, Wise C. Ketamine in Neurosurgical Procedures. Lancet. 1971;1(7688):40–1.

12. Shapiro HM, Wyte SR, Harris AB. Ketamine Anaesthesia in Patients with Intracranial Pathology. Br J Anaesth. 1972;44(11):1200–4.

13. Wyte SR, Shapiro HM, Turner P, Harris AB. Ketamine-Induced Intracranial Hypertension. Anaesthesiol Intensive Ther. 1972;36(2):174–6.

14. Gardner AE, Dannemiller FJ, Dean D. Intracranial Cerebrospinal Fluid Pressure in Man During Ketamine Anaesthesia. Anesth Analg. 1972;51(5):741–5.

15. Albanese J, Arnaud S, Rey M, Thomacot L, Alliez B, Martin C. Ketamine Decreases Intracranial Pressure and Electroencephalographic Activity in Traumatic Brain Injury During Propofol Sedation. Anaesthesiol Intensive Ther. 1997;87(6):1328.

16. Gardner AE, Olsen BE, Lichtiger M. Cerebrospinal-fluid Pressure During Dissociative Anesthesia with Ketamine. Anaesthesiol Intensive Ther. 1971;226–8.

17. Filanovsky Y, Miller P, Kao J. Myth: Ketamine Should not be used as an Induction Agent for Intubation in Patients with Head Injury. JCMU. 2010;12(2).

18. Zeiler FA, Teitelbaum J, West M, Gillman LM. The Ketamine Effect on ICP in Traumatic Brain Injury. Neurocrit Care. 2014;21:152–73.

19. 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.

20. Miller RD. Miller's Anaesthesia. New York: Elsevier/Churchill Livingstone; 2005. 346-348 p.

21. Flower O, Hellings S. Sedation in Traumatic Brain Injury. Emerg Med Int. 2012;

22. Himmelseher S, Durieux ME. Revising a Dogma: Ketamine for Patients with Neurological Injury? Anesth Analg. 2005;101(2):524.

23. Sibley A, Mackenzie M, Bawden J, Antsett D, Villa-Roel C, Rowe BH. A Prospective Review of the use of Ketamine to Facilitate Endotracheal Intubation in the Helicopter Emergency Medical Services (HEMS) Setting. Emerg Med J. 2011;28:521–5.

24. Cromartie RS. Rapid Anaethesia Induction in Combat Casualties with Full Stomachs. Anesth Analg. 1976;55:74–6.

25. Dinsmore J. Traumatic brain injury: an evidence-based review of management. 2013; Available from: http://dx.doi.org/10.1093/bjaceaccp/mkt010

26. Norman R, Matzopoulos R, Groenewald P, Bradshaw D. WHO | The high burden of injuries in South Africa [Internet]. World Health Organisation. World Health Organization; 2011 [cited 2016 Sep 14]. Available from: http://www.who.int/bulletin/volumes/85/9/06-037184/en/

27. Kangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence Summaries: The Evolution of a Rapid Review Approach. Syst Rev. 2012;1(10).

28. Ganann, et. al. Expediting Systematic Reviews: Methods and Implications of Rapid Reviews. Implement Sci. 2010;5(56).

29. Fletcher RH. Clinical Practice Guidelines [Internet]. UpToDate.com. Available from: www.UptoDate.com

30. Graham R, Mancher M, Wolman DM, Others. Clinical Practice Guidelines We Can Trust. Institute of Medicine, Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Washington, DC: National Academies Press; 2011.

31. Grant MJ, Booth AA. A Typology of Reviews: An Analysis of 14 Review Types and their Associated Review Types. Health Info Libr J. 2009;26:91–108.

32. Khan KS, Kunz R, Kleijnen J, Antes G. Five Steps to Conducting a Systematic Review. J R Soc Med. 2003;96(3):118–21.

33. Russel R, Chung M, Balk EM, et. al. Issues and Challenges in Conducting Systematic Reviews to Support Development of Nutrient Reference Values: Workshop Summary. In: Nutrition Research Series. Rockville: Agency for Healthcare Research and Quality; 2009. (Vol 2).

34. Brain Trauma Foundation. Management and Prognosis of Severe Traumatic Brain Injury. New

York: Brain Trauma Foundation; 2000.

35. Vos PE, Battistin L, Birbamer G, et. al. EFNS Guideline on Mild Traumatic Brain Injury: Report of an EFNS Task Force. Eur J Neurol. 2002;9:207–19.

36. Caro D, Walls RM, Grayzel J. Sedation or Induction Agents for Rapid Sequence Intubation in Adults. UpToDate. 2015;

37. Smith BJM. A Review of Etomidate for Rapid Sequence Intubation in the Emergency Department. J Emerg Med. 1997;15(2):221.

38. McGillicuddy DC, De La Pena J, Goudie JS, et. al. Adherence to Dose of Succinylcholine and Etomidate in the Emergency Department. West J Emerg Med. 2010;10(5):432–4.

39. Wells M. Emergency Medicine Society of South Africa Practice Guideline: Rapid Sequence Intubation. 2010;

40. Lafferty KA. Medications used in Tracheal Intubation. Medscape. 2015;

41. Driver B, Moore J, Reardon R, Steinberg L, Antoclick A, Usher S, et al. Ketamine versus Etomidate for ED Rapid Sequence Intubation. Conference Abstract. 2014;21(5).

42. Higgins J. The Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomised Trials. BMJ. 2011;343.

43. AGREE Collaboration. Development and Validation of an International Appraisal Instrument for Assessing the Quality of Clinical Practice Guidelines: The AGREE Project. Qual Saf Health Care. 2003;12(1):18–23.

44. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: A Measurement Tool to Assess the Methodological Quality of Systematic Reviews. BMC Med Res Methodol. 2007;7(10).

45. Sharif M, Sharif FNJ, Ali H, Ahmed F. Systematic Reviews Explained: AMSTAR - How to Tell the Good From The Bad and the Ugly. ODHM. 2013;12(1).

46. Gonzales-Suarez CB, Grimmer-Somers K, Dizon JM, et. al. The PEDro Scale is a Valid Measure of the Methodological Quality of Clinical Trials: A Demographic Study. Journal of Healthcare Leadership. 2012;4:141–56.

47. Gonzalez-Suarez CB, Grimmer-Somers K, et al. Contextualising Western Guidelines for Stroke and Low Back Pain to a Developing Country (Philippines): An Innovative Approach to Putting Evidence into Practice Efficiently. Journal of Healthcare Leadership. 2012;4:141–56.

48. Coleman K, Norris S, Weston A, et. al. NHMRC Additional Levels of Evidence and Grades of Recommendations for Developers and Guidelines: Stage 2 Consultation. NHMRC. 2009;1–21.

49. Deeks J. Altman D. BM. Systematic Reviews in Healthcare: Meta-analysis in Context. London: BMJ Publication Group; 2001. (Second Edition).

50. Jensen AG, Callesen T, Hagemo JS, Hreinsson K, Lund V, Nordmark J, et al. Scandinavian clinical

practice guidelines on general anaesthesia for emergency situations. Acta Anaesthesiol Scand. 2010 Sep;54(8):922–50.

51. Cohen L, Athaide V, Wickham ME, Doyle-Waters MM, Rose NGW, Hohl CM. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. Ann Emerg Med. 2015 Jan;65(1):43–51.e2.

52. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med. 2011 May;57(5):449–61.

53. Mayglothling J, Duane TM, Gibbs M, McCunn M, Legome E, Eastman AL, et al. Emergency tracheal intubation immediately following traumatic injury: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012 Nov;73(5 Suppl 4):S333–40.

54. Bell DD, Brindley PG, Forrest D, Al Muslim O, Zygun D. Management following resuscitation from cardiac arrest: recommendations from the 2003 Rocky Mountain Critical Care Conference. Can J Anaesth. 2005 Mar;52(3):309–22.

55. Wang X, Ding X, Tong Y, Zong J, Zhao X, Ren H, et al. Ketamine does not increase intracranial pressure compared with opioids: meta-analysis of randomized controlled trials. J Anesth. 2014 Dec;28(6):821–7.

56. Jabre P, Combes X, Lapostolle F, Dhaouadi M, Ricard-Hibon A, Vivien B, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. Lancet. 2009 Jul 25;374(9686):293–300.