A RETROSPECTIVE REVIEW OF POST-INTUBATION SEDATION AND ANALGESIA PRACTICES IN A SOUTH AFRICAN PRIVATE AMBULANCE SERVICE

by

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**Abbreviations**

ALS – Advanced Life Support

BLS – Basic Life Support

BP – Blood Pressure

CCA – Critical Care Assistant

DBP – Diastolic Blood Pressure

DS – deep sedation

EC – Emergency centre

ECP – Emergency Care Practitioner

ECT – Emergency Care Technician

EMS – Emergency medical services

ETI – Endo-tracheal intubation

ETT – Endo-tracheal Tube

GCS – Glasgow Coma Score

HR – Heart rate

ICU – Intensive Care Unit

ILS – Intermediate Life support

MAP – Mean Arterial Pressure

NDip – National Diploma

N MBA – Neuromuscular blocking agent

PISA – Post Intubation sedation and analgesia
PRF – Patient Report Form

RCT – Randomized Control Trial

RSI – Rapid Sequence Intubation

RASS – Richmond Agitation Sedation Scale

SBP – Systolic Blood Pressure
PART A: LITERATURE REVIEW
**Background**

Practitioners working within the EMS in South Africa have various qualifications, each with a different scope of practice (1,2). These qualifications include Basic Life Support (BLS), Intermediate Life Support (ILS), Emergency Care Technicians (ECT), Emergency Care Assistant (ECA) and Advanced Life Support (ALS). The ALS qualification is divided into the Critical Care Assistants (CCA: 11-month short course), National Diploma (NDip: three-year university diploma) and Emergency Care Practitioners (ECP: four-year university degree). The South African government recommends that there be at least two medically trained practitioners on an ambulance unit (usually an ILS and a BLS) and one ALS practitioner on a primary response vehicle (1). If the patient requires the care of the ALS practitioner, the response vehicle will need to be driven by one of the crew operating in the ambulance unit. This leaves only one individual caring for a critical patient at a time during patient transport.

Emergency pre-hospital intubation is one of the skills performed by trained ALS practitioners. (3,4). Endotracheal intubation and mechanical ventilation are extremely uncomfortable and anxiety-provoking procedures for patients (5). Inadequate sedation and analgesia during intubation and mechanical ventilation (especially when pharmacologically paralysed) may lead to increased catecholamine release and a multitude of undesirable effects (6–8). It is therefore important to continue sedation and analgesia administration during the post-intubation period. In order to improve on patient care during this period, it is important to assess the current practice that is being employed in the pre-hospital setting.

South Africa is classified as a low to middle income developing country with a significantly higher burden of trauma morbidity and mortality than the global average (9). A large portion of the population lives in rural regions where medical facilities are far apart. The emergency medical services (EMS), which renders pre-hospital medical care, have limited capacity; especially in the rural regions and are therefore often over-burdened (9). The EMS in South Africa is divided into the private and government sector (3). People who can afford medical insurance/aid can make use of the private EMS services. Those with limited financial resources have to make use of the government sector EMS which is up to 82% of the South African population, adding considerable constraint to the government’s resources (10).
**Literature review objectives**

In this literature review, post-intubation sedation and analgesia (PISA) practices will be defined. General recommendations for standard and best practice will be described. The current practices in the international Emergency Centre (EC) setting as well as in the pre-hospital setting will be reviewed. Information on guidelines and practices for post-intubation sedation in the intensive care unit (ICU) will be excluded, except for a brief reference regarding the validity of sedation scoring tools.

The literature will also be assessed for information on current pre-hospital PISA practices in the South African setting and whether these practices are in line with current guidelines and international standards (if available).

**Search strategy**

A literature search was conducted on the 27th of May 2020 using the Medical Subject Headings (MeSH) database in PubMed. The following Mesh terms were used for the search strategy.

- Search strategy 1 – “Intubation, intratracheal” AND “Emergency Medical Services” AND “Anaesthesia and analgesia” AND “South Africa” – no results
- Search strategy 2- “Intubation, intratracheal” AND “Emergency Medical Services” AND “Anaesthesia and analgesia” – 163 results

The results obtained from the search were filtered for English text only and limited to the past 15 years. Due to the limited pre-hospital research on the subject and the identification of valuable articles in the reference lists that were older than 10 years, a 15-year range was selected instead of the typical 10-year search range. The results were assessed for relevance according to title. Under each relevant title, the similar article suggestion list was assessed and additional articles were included based on title. The abstracts of these results were reviewed and further elimination was done based on relevance. Full text was reviewed and an additional elimination was done when the research was conducted in the ICU. Only research done in the EC and pre-hospital setting was included. The reference lists of the final count of articles were reviewed for additional titles. Minimal additional articles were obtained in this way. The final number of articles was separated into studies done in the EC and in the pre-hospital setting and will be included in the literature review. The following flow diagram represents the literature search process.
Figure 1A: Literature review process

Articles found through original MeSH term search
n = 163

Articles reviewed for title relevance n = 91

Elimination done by English text and past 15 years
n = 72

Articles reviewed for similar article suggestions n = 40

Elimination done by title relevance n = 51

Similar article suggestions reviewed n = 81

Articles reviewed for abstract relevance n = 121

Elimination after abstract review n = 63

Articles for full text review n = 58

Elimination after full text review n = 25

Pre-hospital articles
n = 7
(n = 2 from reference lists)

n = 5 articles from reference list for additional background information

EC articles n = 21

Exclusion criteria
• Intubation success rate
• Intubation medication
• Ventilation strategies
• Intubation adverse effects
• Procedural sedation for other than intubation
• Educational programs in the EC
Literature review

Introduction

The following literature review will take a look at the practices of PISA. It will include previous and current practices in the pre-hospital setting and EC. The pre-hospital setting includes road operations, aeromedical and inter-facility patient transfers. The discussion will focus on the differences between sedation and analgesia and the benefits of each, sedation scoring tools, long-acting NMBA and the benefits and disadvantages of deep and under sedation. The review will be concluded with PISA practices as recommended by the various articles and guidelines.

Endotracheal intubation

Endotracheal intubation (ETI) is the passing of an endotracheal tube through the mouth or nose and placed beyond the vocal cords into the trachea (11,12). The process of ETI can be facilitated in various ways (11). These include intubation with no medication, typically performed when the patient has no airway reflexes in place such as in cardiac arrest or profoundly obtunded patients. Other ways to facilitate ETI is through pharmacological adjuncts. These include procedural/deep sedation (DS) techniques where a single sedative, induction agent or a combination of pharmacological agents are administered. Another way to facilitate ETI is through Rapid Sequence Intubation (RSI), which is the near simultaneous administration of a potent short-acting induction agent and neuromuscular blocking agent (NMBA) or with a NMBA alone (13,14). Regardless of the technique employed to facilitate endotracheal intubation, pharmacological agents and practice guidelines to ensure continued analgesia and sedation in the post-intubation period should be available to guide any medical practitioner who may perform this procedure (12).

Endotracheal intubation is often performed in the South African pre-hospital setting where transport times to hospital may be prolonged, airway protection is required, and optimisation of oxygenation and ventilation is needed (3,9). The NDip and CCA qualified ALS practitioners were previously licenced to facilitate intubation with deep sedation. This practice was changed recently, and intubation may now only be facilitated by RSI (15).
Only ECPs are licensed to employ RSI (16). Induction agents available in the South African pre-hospital setting include Etomidate and Ketamine, and the NMBA include the short-acting Succinylcholine and the intermediate- to long-acting Rocuronium and Vecuronium (3,4). DS medications to facilitate intubation include Morphine Sulphate and Midazolam.

**Post-intubation sedation and analgesia rationale**

ETI and mechanical ventilation are extremely uncomfortable and anxiety-provoking procedures for the patient (5,17). Additionally, the pre-hospital transport environment presents a unique set of challenges to the intubated patient (18). This includes noise, vibrations, rough terrain and frequent jostling of the patient during transfer from scene to ambulance, from ambulance to EC or from ICU to ambulance for inter-facility transfer. Signs and symptoms of pain and anxiety are therefore common in mechanically ventilated patients. The administration of sedation, analgesia and even long-acting NMBA are important interventions to ensure patient comfort and safety for the patient and crew (14,19).

Inadequate sedation and analgesia administration during and after intubation and mechanical ventilation may lead to increased catecholamine release and a multitude of undesirable effects including tachycardia, hypertension, anxiety, psychological trauma, increased coagulability, myocardial infarction and self-extubation (when the paralysis wears off without adequate sedation) (6–8,20). Additionally, often in the early post intubation period, various other resuscitative procedures are being performed which may exacerbate the patient’s pain and anxiety.

Sedation and analgesia administration are therefore an important part of post-intubation care. It decreases pain and agitation, thereby improving ventilator synchrony and optimising physiological parameters (17,21). Increasing importance is being placed on sedation practices in the acutely injured patient, as this has consequences on long term patient outcome. Inadequate sedation and the resultant physiological responses may increase mortality, hospital length of stay (LOS) and incidence of post-traumatic stress disorder, anxiety, and mental disorders (18,22).
Sedation vs analgesia

It is important to distinguish between analgesia and sedation in terms of post-intubation medication administration. Analgesia is administered for pain relief since ETI and mechanical ventilation are uncomfortable and painful procedures (23). Opioids are often used as analgesics. Sedation is administered to decrease agitation and anxiety during the intubation and mechanical ventilation process. The commonly used sedatives have minimal or no analgesic properties.

Adequate analgesia in the intubated patient is more important than large doses of sedation and anxiolysis (8). The Society of Critical Care Medicine advocate analgesia first or even analgesia only sedation (termed analgosedation) during mechanical ventilation with dosing being determined by validated sedation scoring tools (6,15) Analgosedation is the administration of analgesics (mainly in the form of opioids) without concomitant administration of sedatives or anxiolytics. Since opioids have some sedative effects, adequate analgesia administration will result in patient sedation and comfort without actual sedation administration (24). Sedation should only be added if appropriate amounts of analgesia does not relieve the anxiety. Literature shows that adequate analgesia leads to less need for sedation. Less sedation results in decreased adverse effects such as prolonged ventilation and higher hospital LOS (15).

Common barriers to good PISA administration include the belief that intubated patients only need sedation and no analgesia, the belief that some sedative-only agents provide analgesia, the belief that analgesic agents cause more severe hypotension than sedatives alone, and the time it would take to initiate analgesia infusions (25). Pre- and post-intubation hypotension is a particularly high risk factor resulting in poor post-intubation sedation and analgesia administration, due to the pharmacodynamic effect of these agents on haemodynamics (12,14).

The effects of sedation on haemodynamics may be more pronounced in the pre-hospital setting than the in-hospital setting (14,26,27). Particularly in the trauma patient, this has been associated with poor outcomes and is therefore a valid hindrance to analgesia and sedation administration. A 2014 retrospective descriptive study was done in the South African pre-hospital setting by Stassen et al, evaluating the prevalence of hypotension and hypoxemia in traumatic brain injuries (TBI) (27). Hypotension was classified as a systolic blood pressure of less than 90mmHg and this was seen in 27.3% of patients upon first presentation. A third of the patients had at least one hypotensive episode during the pre-hospital period.
It was found that Midazolam administration had a greater association with hypotension in TBI patients than Morphine, which had no significant association (27). The overall mean dose of Midazolam was also higher than the mean Morphine dose administered. Only blunt force TBI patients with a Glasgow Coma Score (GCS) of less than 13 were included in this study and may have presented with other concomitant injuries. A strong association was found between the incidence of hypotension and the patient’s injuries, with 86.7% of patients presenting with injuries that could be the cause of hypotension. It can therefore be extrapolated that trauma cases have a real concern for hypotension and is therefore a valid reason for medical practitioners to be weary of PISA administration. Since there is such a large burden of trauma-related injuries in South Africa, careful titration is needed to mitigate this risk whilst addressing sedation and analgesia requirements (14,28).

Sedation and analgesia scoring tools

The Society of Critical Care Medicine recommends that intubated patients be assessed for pain and agitation using a validated pain and sedation assessment scoring tool (23,29). Sedation and analgesia can then be administered and/or titrated accordingly, following the outcome of these assessments. It is rare that a sedation scoring tool is utilised in the emergency setting and currently medical practitioners rely on physiological and behavioural indicators to determine the need for sedation and analgesia (20). Physiological indicators include vital signs such as elevated heart rate, respiratory rate and blood pressure. Behavioural indicators include patient movement, facial expression and poor ventilator synchrony. Agitation can result from inappropriate levels of sedation as well as physiological causes such as pain, hemodynamic instability, hypoxia or delirium. Similarly, other medications and the patient’s underlying illness or injury, both in the acute and chronic context, influence physiological indicators, and thus these indicators cannot be used exclusively to determine the degree of patient agitation (22,30).

Sedation assessment scoring tools cannot be used on patients who have received NMBA, a common practice in emergency airway management. Since these scoring tools rely on patient response to stimulation this is not possible in the pharmacologically paralyzed patient (18). Since numerous patients receive long-acting NMBA agents in the pre-hospital setting for the safety of the patient and crew, these scoring tools cannot be used on these patients. The jostling, vibration and noise that is present in the pre-hospital transport environment may also make the assessment using these scoring tools challenging, even in patients not under the influence of long-acting NMBA.
For these reasons, these tools would be ineffective in measuring sedation levels in the pre-hospital setting. After initial stabilization, the implementation of a sedation scoring tool may be considered. This process may not be completed in the pre-hospital setting. This further applies in the EC when multiple life-saving interventions are being employed, most of which will agitate the patient, rendering a sedation scoring tool ineffective and redundant. It may however be feasibly in the pre-hospital transfer setting, after a patient has been stabilised and is being transferred to a different medical facility and no active interventions that will rouse the patient is being performed.

The most common assessment of sedation level used in the EC and in the pre-hospital setting is the GCS, which was not originally designed nor validated to measure sedation and analgesia requirements (31). The Richmond Agitation Sedation scale (RASS) has been used in some aeromedical transport settings, however, the use of this has been found to be inconsistent as well (18). Despite the numerous sedation assessment scoring tools available, there is no consensus about the gold standard (8).

**Sedation and analgesia goals and recommendations**

Early goal directed (EGD) PISA is the initiation of therapy to achieve as light a level of sedation as clinically possible and as early as possible (within 2 hours after intubation) (32). The sedation and analgesia levels should be titrated to the lowest dose to maintain patient comfort, safety and ventilator synchrony (23). This is to optimise sedation early on to prevent prolonged and inappropriate deep sedation in the ICU, improving long term outcomes of patients (17).

Lighter sedation is difficult to initiate and maintain in the pre-hospital post-intubation period, due to the inherent nature of pre-hospital medical care, and the acuity of the patient (21). An overshoot of sedation administration is inevitable. EGD sedation can however be initiated as soon as possible after the patient has been stabilised. EGD sedation has not been studied in the EC or pre-hospital setting yet, therefore no recommendations can be made regarding the appropriate score or goal for whichever tool is used (21). EGD post-intubation analgesia and sedation is difficult to determine since it needs to be individualised to each patient. As long as the sedation goal is defined early for each patient and re-evaluated as needed, then the actual value of the sedation or analgesia score thereof is irrelevant in the emergency setting (32,33). EGD PISA should be implemented into the RSI or intubation protocol as a whole with dosage recommendations, leaving less up to the medical practitioner’s discretion (32).
Deep sedation

DS in the early post-intubation period carries its own unique risks (18,21). Deeper sedation in the intubated patient, whether long term or in the early post-intubation period in the emergency setting has been associated with increased mortality, hospital LOS, longer ventilation days and delirium. Benzodiazepine use has been specifically linked to this outcome and its increased risk of delirium and long-term neurological compromise (23). Deeper levels of sedation creates the risk of depressing patients’ protective airway reflexes which may lead to insidious regurgitation of gastric contents (31). This may create long term complications such as pneumonia, contributing to an increase mortality rate.

A systematic review and meta-analysis by Stephens et al recently found that a range of 19.6% to 80.6% with a mean of 34.7% of patients are deeply sedated within the first 48 hours of mechanical ventilation initiation (34). There were nine studies included in this review, of which two were randomized control trials (RCT) with low risk of bias and seven were high quality observational studies. Only two of the studies included data from the patients during their EC stay. The study found that early DS resulted in increased in-hospital mortality, ventilator days and ICU LOS. Due to the lack of RCTs on the subject and in this study, there may have been confounding influences present. This may include more severely ill or injured patients having lower sedation scores due to their illness or injury rather than the sedation administered. Similarly, their outcome could have been due to their conditions rather than the earlier DS. Only two studies reported illness severity and no subgroup analyses were done on these studies to account for this confounder, since different illness severity scores were used in these studies. One study used a GCS score of less than 9 to assess sedation depth and the remaining studies used the RASS score of less than -3. This reflects the differences in practice between institutions. This study did not include sedation practices from the pre-hospital setting. It is therefore hard to extrapolate the results and conclude that sedation practices in patients in the pre-hospital and EC setting will have a similar long-term outcome, since the sedation practices will be different in these environments than in the controlled and quiet ICU setting. This meta-analysis did reflect real world practice and potential associations though, and it reiterates the importance of mindful post-intubation care early on, including in the pre-hospital environment and the EC. Early DS in the initial period of intubation can lead to an overshoot of sedation that lasts into the ICU stay and can be a modifiable factor on patient outcome (34).
In a 2019 study done by Fuller et al, assessing the long-term outcomes of sedation practices in the EC, they found that the majority of patients were either deeply sedated (52.8%) or they received no sedation or analgesia at all (10.8%) (35). The deeply sedated patients were more likely to have poor neurological outcome in terms of acute brain dysfunction. This is significant since patients with neurological injury were excluded from the study population, therefore this neurological dysfunction could not be attributed to the injury itself. DS was classified as a GCS of less than 9 or a RASS score of between -3 and -5. It is unclear if this is due to the deeper sedation levels or the underlying illness or injury that gave the appearance of a deeper sedation level. The deeper EC sedation level carried over into the ICU for up to 48 hours. The implementation of EGD PISA in the EC may prevent this overshoot or at least shorten the length of time the patient remains in this deeply sedated state. Since the GCS score was also assessed, this study may potentially be generalisable to the pre-hospital setting, where the GCS is used, despite the invalid nature of this use. This study demonstrates that EGD post-intubation sedation and analgesia in the intubated patient in the EC may result in earlier appropriate sedation levels in the ICU.

These results also indicate that despite improvements in sedation practices in the EC, there is still no standardized protocol for the initiation and maintenance of sedation in the early intubation period. The authors of the study acknowledged the staff challenges and need for constant monitoring of patients to obtain an appropriate sedation level in the EC, which makes it challenging. This challenge extends to the pre-hospital setting where there is often only one medical practitioner treating and monitoring the patient in the back of the transport vehicle (1). This practitioner needs to perform multiple tasks to maintain stability of the patient, and monitoring of sedation and analgesia levels may be neglected in the midst of this.

Moderate to deeper sedation in the aeromedical transport environment has been associated with increased hospital LOS (18). A retrospective study published by George et al in 2020 evaluating the in-hospital long-term outcome of patients who underwent DS after intubation in the pre-hospital environment, assessed medication selection, DS levels and dosing of sedation and analgesia during aeromedical transport (18). The sedation depth was calculated using the RASS score. The dosing of sedation was classified by two pharmacists, blinded to the outcomes of the study, as low, intermediate and high upon assessment of the documentation according to pre-set criteria.
The primary outcome was hospital LOS and secondary outcomes were ventilator free days, delirium and mortality. The primary outcome was evaluated descriptively since it was a continuous variable whereas the secondary outcomes, which were binary, were evaluated with logistic regression to account for confounding. The study was adequately powered with an inclusion of 327 patient records after a power calculation indicated the need for at least 276 patients to have a power of 80%. All results were presented in terms of the RASS score as well as the sedation level according to the pharmacists. The results were similar in both categories. The study found an increased hospital LOS with higher levels of pre-hospital sedation depth with an increase between mild, moderate and deep sedation of 14%, 78% and 51% respectively, when compared to patients receiving no sedation. It is unclear if the patients had a shorter LOS due to an increase mortality rate or due to a better outcome. The authors failed to determine if this was due to the lingering effects of the pre-hospital sedation or due to the severity of the patient’s condition. The use of benzodiazepines was significantly associated with hospital LOS with an increase of 2.6 days in the patients who had received a benzodiazepine which accounted for a 36% increase in hospital LOS. What was interesting to note was that moderate sedation accounted for the longest hospital LOS and the least ventilator free days.

Unfortunately, the patients’ illness or injury severity were not taken into account and it is therefore unclear whether the more injured patients with the worst prognosis was either deeply sedated or not sedated at all and had a higher mortality rate which accounted for the shorter hospital LOS. On the other hand, the patients with the best prognosis only needed moderate sedation but longer recovery times (since they did not contribute to the mortality rate) which accounted for longer LOS and less ventilator free days. This could not be determined from the study. No statistical significance was found between the levels of sedation and the development of delirium or in-hospital mortality, after accounting for the confounder of neurological injury. Patients who received no sedation had the highest risk of in-hospital mortality at 33.9% (odds ratio not reported) but this was more likely due to the severity of their conditions not requiring sedation since two thirds of the 37% overall mortality did receive some type of sedation. It could also have been due to the adverse effects of no sedation such as agitation and increased catecholamine release, and the physiological effects of that on the patient’s condition. This is unfortunately noted as a significant confounder in this study, since the severity of the patients’ illness or injuries were not accounted for. The patients were only classified into neurological and non-neurological injury as the reason for intubation. The severity was not classified.
The primary outcome of hospital LOS may have been due to either the patients’ injury or to the level of pre-hospital sedation. The authors found high variability in the choice and combination of medications used during transport and hypothesised that this may be due to lack of stringent sedation protocols.

A similar situation exists in the South African pre-hospital setting where the decision as to medication type and dose is highly practitioner dependent with only guidelines and no strict protocols for these procedures (36). According to the authors, it appears that pre-hospital sedation agent choice and level of sedation have less of an impact on in-hospital outcomes such as delirium and mortality than the longer-term use of these in the EC and ICU. The question still remains if the use of these medication in the EC and ICU did not also have an effect on the primary outcome of the study, since it was not taken into account. Despite the rigorous study design and analysis of the results, potential short-comings of this study was therefore the fact that EC and ICU medication administration was not taken into account due to limited time and resources.

**Under-sedation**

In a large study done by Weingart et al in 2013, evaluating the PISA practices in US ECs, it was found that more than half of patients intubated in the EC did not receive PISA (8). They evaluated the characteristics of patients who were most likely to receive sedation and these included those that survived to admission. This may indicate that patients were less ill or injured and therefore more awake and in greater need for sedation and analgesia during their EC stay. Another conclusion may be that some patients died prior to sedation or analgesia requirement or that they were intubated during an unsuccessful resuscitation. Patients who were less likely to receive post-intubation sedation included patients with cardiac disease or a circulatory abnormality. The concerns for haemodynamic instability would account for these patients being less likely to receive sedation or analgesia. The study design and analysis of the results appears to be fairly rudimentary, with minimal exclusion criteria and sub-group analyses, but the sample size was over 1.07million patients, therefore the resultant estimates give a good indication of current practice. The authors also found that there was an increase in PISA administrations in patients over the four-year study period. This alludes to the possibility that more focus is being placed on post-intubation care (8).
An analgesia first regimen for post-intubation sedation care has been suggested and shown to decrease sedative use, especially benzodiazepines (8,25). The sedation goal is reached faster with this approach and there is a decrease in ventilator days and hospital LOS (8). Unfortunately, in the above-mentioned study by Weingart et al, it was found that up to 75% of patients did not receiving an opioid post intubation during their EC stay at all. Current EC guidelines for PISA recommends analgesia in the form of an opioid first, before anxiolysis in the form of benzodiazepines sedation (25). Ideally this should be started as soon as possible after the completion of intubation, before the induction agent wears off, especially if the patient had received a long-acting NMBA. This strategy has been shown to decrease mortality in the patients with an extended EC stay as well as decreases benzodiazepine use and shorter ventilator days (8,30).

A concern in the pre-hospital transport setting for undersedation is the safety risk to the agitated patient (18). These patients have a higher risk for self-extubation or accidentally removing indwelling lines and catheters by the agitated patient themself which may be challenging to replace in the close confines of the transport vehicle (14).

Neuromuscular blocking agent use and sedation

Long-acting NMBA can be used for the procedure of RSI as well as for continued paralysis post-intubation (22). Benefits of long-acting NMBA include better ventilator synchrony, prevention of patient-self extubation or when succinylcholine is contra-indicated. During pre-hospital transport, long-acting NMBA are often administered to prevent patient movement, ensure safety in transport of the patient and crew, decrease oxygen requirements and enable better ventilator synchrony (14,19,22,37).

Historically, a common indication for the administration of sedation was purported to be patient movement, a sign that is masked by NMBA (22). Patients at risk of awake paralysis is twice as high in patients who received NMBA (22). Due to the false sense of sedation in a paralysed, immobile patient, long-acting NMBA administration have been associated with delays in initiation of as well as lower doses of post-intubation sedation. It is reported that this awake paralysis may lead to an increase in catecholamine release which in turn will increase heart rate and blood pressure. These are classic indications for medical staff to administer additional sedation (7,19). Since long-acting NMBA may have a duration of action between 30 and 75 minutes, depending on the dose (6,7), it is important that these patients are adequately sedated when long-acting NMBA are administered to prevent a situation where a patient is pharmacologically paralysed with a degree of awareness.
Anaesthesiologists have classified death as the only complication worse than the scenario of wakeful paralysis. Various descriptions by patients of awake paralysis have been reported and include feelings of being buried alive, suffocation, panic and anxiety, powerlessness and impending death (22). These can result in post-traumatic stress disorder and lasting anxiety and mental disorders. These consequences will be augmented in patients with higher levels of consciousness prior to induction and intubation. Therefore, the balance between over and under sedation needs to be managed (13).

In a 2013 study done by Watt et al, it was found that there was delay to post-intubation sedation administration in patients who receive Rocuronium during RSI (38). They found that, following the use of Etomidate as the induction agent, the mean time to post-intubation sedation was 27 minutes, leaving these patients without sedation for approximately 20 minutes. Patients who were not intubated using Etomidate or who did not require post-intubation sedation were excluded from the study. The patients included in the study therefore presented with a higher level of consciousness which makes the results significant since these patients were left without sedation when they indeed required it. They proposed that the delay in sedation administration may be multifactorial due to the logistics of obtaining and setting up the sedation. This barrier may be generalised to the pre-hospital setting since there is often a limited number of medical practitioners caring for a patient in the back of a transport vehicle, with one for ambulances and possibly two for aeromedical transport. These practitioners are often overburdened with performing multiple life-saving tasks and PISA administration or setting up of an infusion may therefore be delayed. They further suggested that better access and pre-planning of post-intubation sedation should be implemented in hospital policy.

A similar 2014 EC study done by Korinek et al, assessed the timing and dosing of post-intubation sedation when patients were intubated with Succinylcholine and Etomidate as compared with Rocuronium and Etomidate (39). They hypothesized that since Etomidate and Succinylcholine has similar duration of actions, which is less than 6 minutes, the renewed movement of patients will prompt for sedation faster in this patient group. They also hypothesised that the amount of sedation will be titrated higher than in the Rocuronium and Etomidate group since the ability to assess the need for and adequacy of sedation is easier and can be done sooner in the Succinylcholine group. They found that patients in the Succinylcholine group receive higher levels of sedation, which lead to the belief that the patients in the Rocuronium group is under-sedated for the duration of their paralysis.
Thus, patient behavioural factors may be a stronger indicator for awareness than the physiological factors.

In a retrospective study by Johnson et al in 2015, they found that patients who received Rocuronium during RSI had a significantly longer time to post-intubation sedation with the time to sedation in the Succinylcholine group being 16 min and in the Rocuronium group 34 min (6). They also compared the time difference to sedation or analgesia administration when an emergency pharmacist was and was not present in the EC during and after the intubation process. They found that when a pharmacist was and was not present, the average time was 20 minutes and 49 minutes to sedation or analgesia administration, respectively. In the presence of a pharmacist, the time difference to 1st sedation or analgesia between the Rocuronium and Succinylcholine groups was 23 and 12 minutes respectively. In the absence of the pharmacist the difference was 55 and 28 minutes respectively. The majority of the patients (77%) received Etomidate as the induction agent and the remainder received variations of Ketamine, Midazolam or Propofol. All of these induction agents had shorter duration of actions than Rocuronium. The mean GCS of the patients in the Rocuronium group was 13, indicating inappropriate practice, where patients were under the influence of a long-acting NMBA without adequate sedation and analgesia. This raises the concern that patient behavioural factors alert medical staff to their wakefulness instead of sedation and analgesia being administered according to an approved protocol. Time to sedation or analgesia was limited to initiation of infusions and did not take bolus dose administrations into account. The time delays may therefore have been over-estimated if a bolus dose sedation or analgesia was administered prior to the start of the infusion. The dosages were not reported on and the adequacy of the sedation or analgesia cannot be commented on. No blood pressure measurements were reported or analysed thus the potential withholding of sedation and analgesia in relation to hypotension could also not be analysed. The hypothesis in this study that a dedicated team member, i.e., the emergency pharmacist, whose sole focus is the PISA care of the patient, will reduce the time to these treatments, proved to be true in this study. This reiterates the challenge in the pre-hospital setting where there is often only one medical practitioner caring for the patient during the post-intubation period.
In contrast to the above-mentioned study, an EC study done by Kilber et al/ in 2018 evaluated the number of sedation and/or analgesia interventions administered early and late post-RSI with Etomidate and Rocuronium only (13). They grouped the early intervention into a time range of 0-30 minutes and the late group into 60-90 minutes. The reason behind these time frames were to assess if patients receive early PISA as a standard or only when the Rocuronium starts wearing off after approximately 60 minutes and the subsequent movement of the patient then prompts additional sedation. They also assessed the time to 1st sedation and analgesia. They found that most patients received early post-intubation sedation with a median of 2 interventions in the early phase versus 1 in the late phase. This concluded that patients were adequately sedated when a long-acting NMBA was administered. They also found that the starting sedation infusion in the EC is much higher than the same starting sedation type in the ICU. This led to the authors’ conclusion that patients were more deeply sedated in the EC setting. These patients need to undergo a multitude of procedures in a short amount of time to determine the level of illness or the extent of the injuries, therefore may also require deeper levels of sedation to maintain patient comfort and safety. The authors also preferred to overstate the need for sedation when patients were under the influence of long-acting NMBA. They found that the average time to post-intubation sedation was 8 minutes. They compared this to a similar study they conducted several years ago and this time has significantly improved. This was most likely due to active steps that were taken since the previous study, in educating the EC staff during conferences, at the bedside and during shift handovers. This highlights the importance and effectiveness of protocol revision and education for patient care improvement (13).

In a 2019 study by Lembersky et al/ assessing post-intubation sedation practices, it was found that up to 86.4% of patients received post-intubation sedation, excluding patients in cardiac arrest or those who may have had reason to have sedation withheld (25). These reasons included pre- and post-intubation hypotension as well as patients with head injuries with haemorrhage where sedation was withheld in order to conduct neurological examinations. This rate is higher than previously reported, supporting the fact that sedation practices post-intubation is improving (8). Unfortunately, there were still up to 11.8% of cases where patients had received a long-acting NMBA without concomitant sedation for more than 15min after the intubation. These findings suggest that short acting NMBA may be preferable to decrease the incidence of wakeful paralysis. Patient movement is an inappropriate clinical sign to administer sedation, especially if they had received a long-acting NMBA.
It appears from the above studies that there are still large numbers of patients that go without post-intubation sedation after long-acting NMBA were administered. The study by Kibler et al that found this not to be the case, concluded that protocols implemented after a previous study in the same EC, may have mitigated this problem (13). This reiterates the fact that protocols regarding PISA is lacking, but effective if implemented. The majority of the studies discussed expressed a concern for under-sedation, or patients being pharmacologically paralysed without adequate sedation and analgesia. Research to assess if this is the case in reality is therefore important before changes to protocols or new guidelines can be implemented. Limited studies regarding PISA practices exist in the South African setting and research is needed to assess if there is a similar problem and lack of protocols in this setting.

Current pre-hospital practice

There has been an increase in EC boarding over recent years (23,28,40–42). This means that critically ill patients remain in the EC for an extended period of time while waiting for an ICU bed. The high burden of trauma-related injuries in South Africa contributes to the burden on the EC. EMS are often turned away from an EC to transport patients to neighbouring hospitals when the EC is overcrowded or no ICU beds are available. This leads to a greater delay in definitive care for the critically ill, where an increase in EC LOS already results in an increased mortality of critically ill patients (8,15,31). The potential increase in pre-hospital transport times and increased EC boarding reiterates the importance of optimizing post-intubation care including sedation and analgesia practices.

The Health Professions Council of South Africa (HPCSA) is the governing body for the medical community, including pre-hospital emergency care providers in South Africa. The HPCSA updated its clinical practice guidelines in 2018, however post-intubation sedation recommendations are fairly vague. The guidelines are limited to the sedation practices of intubated patients with certain disease conditions such as asthma or sepsis (15). No recommendations are made regarding medication type or dosage. This leaves the choice to the practitioner. The Emergency Medicine Society of South Africa (EMSSA) released clinical practice guidelines in 2012 for procedural sedation and RSI (36). In these guidelines, the post-intubation recommendation is administration of analgesia in the form of Morphine Sulphate at a dose of 1-2mg every 10 minutes, titrated to effect, and/or sedation in the form of Midazolam at 1-2mg every 10minutes, titrated to effect. The phrase titrate to effect seems ambiguous and no mention is made as to the goal of therapy and this therefore leaves a great deal to the discretion of the ECP.
There is a lack of research into the pre-hospital post-intubation sedation practices, internationally and in South Africa. The majority of studies look at the procedure of RSI, the feasibility and validity thereof in the pre-hospital setting or intubation success rates in general (3,4,26,43–46).

In 2006, a retrospective study was done by Frakes et al in an aeromedical setting. They aimed to determine if patients under the influence of a long-acting NMBA receive sedation or analgesia and to determine if there were common factors amongst those who did not. It was determined that 91% of patients who received a long-acting NMBA pre-hospital, was given some sort of sedation or analgesia as well (22). This was determined by independent flight nurses reviewing the charts of the patient sample and concluding on pre-set criteria based on medication onset and duration of action, whether the patients were under the influence of sedation or analgesia. The time and doses of these interventions were not reported and the adequacy of the sedation could not be determined. No significant correlation was found between sedation or analgesia administration and the potential common factors that were evaluated, which were gender, age, systolic blood pressure, diagnosis and flight nurse experience. The results demonstrate a high rate of sedation administration, however, if the timing and dosages were inadequate then the patients may still have experienced wakeful paralysis. The authors did acknowledge the unreliable nature of determining awareness based on the timing of medication administration and duration of action since all patients are different and these indicators may not be applicable to all patients, especially in the noisy aeromedical transport environment. The study was conducted in a single US aeromedical service with individualised protocols and may therefore not be extrapolated to other settings.

A 2009 study done by Singh et al assessing critical events and ventilation practices for acute lung injury patients in the pre-hospital transport setting, commented briefly on the sedation practices during transfer of intubated patients. They found that there were significant in-transit hypotension recorded with the use of sedation administration (26). Post hoc logistic regression analysis revealed that these effects were independently related to female gender, hypotension prior to transfer, NMBA use in transfer and number of sedative administrations. It was also found that 29% of patients received no sedation during transport. The authors suggested this may be due to the large portion of patients with neurological conditions and poor neurological status not requiring sedation or analgesia during transport, or they may have received adequate long-acting sedation prior to transport. No sub-group analysis was done to confirm this hypothesis. The only medications administered that were mentioned in the study was Propofol, Midazolam and Lorazepam.
No mention was made of concomitant analgesia administration. The medical directives and standing orders for the transport agency were included as an appendix in the study and mention was made of analgesia administration for intubated patients, especially those receiving long-acting NMBA. It is unclear if there was in reality no analgesia administration or if it was just not reported on in the study. The majority of the transports were interfacility transfers with only 1.7% transported from an out-of-hospital scene. The medical directive also states that analgesia was to be continued if it was administered in the referring facility. Poor mention was made about initiating analgesia during transport. Since the majority of patients were therefore most likely already stabilised prior to transfer, analgesia may have seemed unnecessary unless the patient had specific painful conditions. This will be different in the case of primary pre-hospital cases since the medical practitioner would have to stabilise the patient and initiate PISA during this time. Due to the small sample of cases where care was initiated in the pre-hospital setting, the full scope of PISA practices in the pre-hospital setting could not be surmised from this study.

Due to the lack of protocols and the uncertain environment of the pre-hospital setting, a single drug for PISA has been suggested by Michetti et al in the pre-hospital setting (12). They performed a study published in 2012 comparing the efficacy of Fentanyl as an agent for analgesia as well as sedation post-RSI. Fentanyl has sedative properties in large enough dosages. Due to the single agent being used, larger doses were needed to obtain a similar sedative effect that is usually obtained with the combination of an opioid and a benzodiazepine. Michetti et al found in their study that Fentanyl, even in large dosages, did not have a significant hemodynamic effect on trauma patients and had a similar sedative effect. They based their assessment of sedation level on the heart rate of the patients, since they postulated that awareness would initially be apparent from an elevated heart rate. This may be flawed already since physiological factors are poorly correlated to sedation level (22). These parameters were measured in the field as well as upon arrival in the trauma bay, directly after the patient was moved and jolted, which can also affect it. More reliable methods for assessing sedation levels, such as brain activity and biometric testing, are not feasible in the pre-hospital setting. Michetti suggested that the added benefit of the Fentanyl only regimen will also cause adequate pain management since the higher dose was needed for a similar sedative effect (12). Unfortunately, the same hypotension was seen with these large doses in comparison to lower doses when added with a benzodiazepine, despite Fentanyl being more hemodynamically stable due to the decrease in histamine release.
The majority of the outcomes of this study were in the short term (hemodynamic factors in the field and in the EC), which decrease the likelihood of confounders. These outcomes included the hemodynamic effects (heart rate and blood pressure) of the two regimens as well as neurological assessment (GCS and pupillary reaction) in the pre-hospital setting and then again in the trauma bay. The different parameters were compared before and after regimen administration and therefore the patients acted as their own controls. Fluid administration was also controlled for during analysis. The only longer-term outcome was the frequency of neurosurgical interventions, which was significantly higher in the Fentanyl only group. The severity of the TBIs were not taken into account though and this could have been a confounder for the higher surgical intervention in the Fentanyl only group. It is unclear if the potentially more severe injury in this group, or the blunting of neurological examination due to the high Fentanyl dose and resultant longer duration of action was the cause for the higher rate of neurosurgical intervention. The study does not add considerable information to PISA practices, except to demonstrate the potential feasibility of Fentanyl only sedation, which may mitigate the long-term adverse effects of Midazolam and make it easier to reach EGD sedation.

In a small pre-hospital US study done in 2013 by Elofson et al, describing the use of long-acting NMBA and post-intubation sedation use in these patients, it was found that patients who received a long-acting NMBA receive post-intubation sedation in a less timely manner than those who were not pharmacologically paralysed, and 21% of these patients did not receive a sedative at all (14). Only patients who required sedation/induction during the RSI procedure were included in the study, and even though accurate GCS values could not be obtained prior to intubation, it could still be deduced that these patients may have experienced some type of awareness as soon as the induction agent wore off, since they needed the induction to begin with. Since Etomidate and Midazolam were used as induction in this study, this time would be between 3 and 5 minutes, and approximately 20min, respectively, after which the patients would experience awareness once more (14). The overall analgesia administration was found to be low, but the group receiving long-acting NMBA did receive more analgesia as compared to those who did not receive a long-acting NMBA. Accurate GCS scores could not be obtained prior to or after intubation. This means that no sedation level assessment was done in the field, post-intubation. Various different agencies were included in the study and mention was made that they had different medications available for use and most likely different guidelines. The study sample size was small, but the data was only presented in a descriptive manner and associations made instead of causation determined.
A US pre-hospital retrospective study in 2019 by Billups et al, compared the time to post-intubation sedation from the time of Etomidate administration, between RSI of patients using Rocuronium and Succinylcholine, respectively (19). The number of sedative interventions post-RSI was also compared. There was no significant difference between the time to post-intubation sedation between RSI using Rocuronium and Succinylcholine found in this study. Despite this, and due to the longer duration of action of Rocuronium, 86.8% of the patients who received Rocuronium was without sedation and therefore pharmacologically paralysed for a time period (ranging from 5 minutes to over 30 minutes) before post-intubation sedation was administered. There was also no difference between the number of sedative doses administered between the two groups. The study setting was pre-hospital and included ground and air transport. The EMS agency involved in the study had protocols in place for the use of RSI as well as PISA. This may explain the similar administration of PISA between the two groups. The authors suggested the reason for the lack of significant differences between the two study groups was due to the study being under-powered. This is possible, since they estimated that to have a power of 80%, both groups needed at least 64 cases. Unfortunately, the exclusion criteria only allowed for 38 patients in the Rocuronium arm and 64 in the Succinylcholine group. This was due to the objectives of the study being very specific and based on a specific intervention. Only patients intubated with RSI using Etomidate as an induction agent and either Rocuronium and Succinylcholine as a NMBA were included. This may have led to a type 2 error of the results where there was no significant difference between time to sedation between the Rocuronium and Succinylcholine groups, where there in fact was a difference. Due to the small sample size, the hypothesis that patients who receive Rocuronium will receive PISA in a less timely manner cannot be accepted or refuted. This study does act as a good inflection point for further research since it is the first study that specifically describes pre-hospital PISA practices. Since not all agencies have the same protocols, it might be interesting to compare this study where protocols regarding PISA practices are in place, to a setting where PISA is up to the discretion of the provider, as is the case in the South African pre-hospital setting.

A study performed by Stein in 2017 investigating student paramedic RSI in Johannesburg is the only South African study commenting on PISA practices that was found during the literature search (4). In this study it was found that only 72% and 63% of patients receive Morphine and Midazolam, respectively, post-intubation. The author of the study suggested deeper analysis of post-intubation care and potential adjustment to protocols used.
All of the above-mentioned studies use similar pre-hospital pharmacological agents during and after the intubation procedure, barring Propofol that is mostly used in the EC setting. It will therefore be possible to draw comparison between practice in these studies and the practices in the South African pre-hospital setting.

**Recommendations**

Due to the risk of awake paralysis, its poor detection in patients and its long-term implications, various organizations have recommended policies to mitigate these risks and manage awareness effectively (22). This includes concurrent administration of sedation and analgesia in patients who receive NMBA in the emergency setting. There is no reliable measure in the emergency setting to detect awareness, rather, there appears to be excessive reliance on clinical signs such as heart rate and blood pressure elevations by healthcare workers which have been shown to be poorly correlated to awareness (22,30). The postulated increase in catecholamine release with subsequent elevations in heart rate and blood pressure may also be detrimental to traumatic injuries, including haemorrhage, elevated intracranial pressure and various conditions sensitive to hypertension (7). The reliance on an elevated heart rate and blood pressure is therefore flawed since it is linked to a myriad of other factors in the trauma patient and not only awareness. It is also harmful to the patient to wait for these apparent physiological indicators of awareness since it is detrimental to the trauma patient’s outcome when it is seen and should rather be prevented altogether.

Current guidelines recommend early administration of post intubation sedation, before the induction agent wears off. It is further advised that a prophylactic loading dose of an opioid be administered immediately after successful intubation and additional sedation titrated after this (23). Protocolising post-intubation sedation is challenging since every patient will have an individual need and goal for the sedation (31). If it is simply to prevent agitation, self harm and self-extubation then a lighter level of sedation can be maintained. However, if it is to obtain a clinical goal such as ventilator control and synchrony, then a deeper sedation level might be required. Since patients respond differently to sedation and achieving a certain neurological status according to a sedation scoring tool is recommended, constant or regular monitoring is required (21,30).
This may be challenging in the pre-hospital setting due to the limited staff resources in the transport vehicle. The sedation goals will also be different depending on the setting, i.e. treatment and transport form a primary scene or an interfacility transfer. The former will potentially require deeper levels of sedation since the patient will still be in the process of being stabilised and these procedures may cause additional pain and agitation, whereas in the transfer setting, the patient will most likely already be stable and will only require lighter levels of sedation and analgesia. These levels will still be different from the ones set in the ICU or even EC setting since the vibrations, noise and jostling of the patient in the transport environment may cause additional agitation and pain which will need to be managed.
Summary and conclusion

PISA practices may play an integral part in the long-term outcomes of patients who are intubated in the emergency setting. Aside from these outcomes, it is also important for patient comfort, to mitigate agitation, anxiety and pain and to optimise hemodynamic factors and ventilator synchrony.

PISA needs to be titrated carefully since deeper sedation may contribute to increased ventilator days, hospital-LOS, delirium and mortality. On the other hand, under-sedation may also contribute to increased mortality, long-term psychological problems and patient discomfort.

There is standardisation of sedation and analgesia protocols in the ICU setting and the titration of sedation is based on validated sedation scoring tools. Due to the unique challenges in the emergency setting, especially pre-hospital, these protocols can unfortunately not simply be adopted in this environment. It can serve as a basis for new policy development though. One that may take into account the challenges in the uncontrolled pre-hospital setting. These protocols advocate adequate sedation and analgesia post-intubation based on a targeted sedation and/or analgesia goal. This goal should ideally be determined using a sedation scoring tool. Unfortunately, no sedation scoring tools have been validated in the pre-hospital setting. There are a few that are being used in this setting though (GCS, RASS, Ramsey), and additional research into its validity may be beneficial.

As can be seen from the growing body of evidence of suboptimal PISA practices in the emergency setting, more attention has been given to postintubation sedation care resulting in an improvement in practice in recent years. There is no dedicated research in the South African pre-hospital setting pertaining to PISA. It is therefore unknown if similar inadequate sedation practices exist in this setting as was seen in the literature review. In order to implement new policies and procedures, current practice must be evaluated first, since improvement cannot be implemented if it is unknown what must be improved. The aim of this study is to evaluate the current South African pre-hospital practice, compare it to best practice standards and current recommendations and evaluate where improvement is needed and make recommendations accordingly.
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48. IBM SPSS Statistics Software subscription.


PART B: MANUSCRIPT IN ARTICLE FORMAT
A RETROSPECTIVE REVIEW OF POST-INTUBATION SEDATION AND ANALGESIA PRACTICES IN A SOUTH AFRICAN PRIVATE AMBULANCE SERVICE

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Abstract

Introduction: Adequate post-intubation sedation and analgesia (PISA) practices are important in the pre-hospital setting where vibration and noise of the transport vehicle may contribute to anxiety and pain in the patient. Inadequate post-intubation practices may lead to long-term detrimental effects in patients. Despite this, these practices are poorly described in the pre-hospital setting. This study aims to describe the current pre-hospital PISA practices in a private South African emergency medical service.

Methodology: Patient report forms (PRF) of intubated patients between 1 Jan 2017 and 31 Dec 2017 from a single private ambulance service were reviewed. Data was analysed descriptively. Correlations were calculated with Spearman’s Rank correlations and group differences were calculated with Independent T tests and Mann-Whitney U tests. Significant correlations were entered into a binomial regression model to determine predictive value of receiving PISA.

Results: The number of PRFs included for analysis was 437. Of these, 69% of patients received some type of PISA. The estimated time from intubation to 1st PISA ranged from 9 to 12 minutes. There were statistically significantly more PISA interventions in patients who had received Rocuronium (p<0.01).
There was weak but significant correlation between the number of interventions and the mean arterial pressure, ($r_s = 0.17$, $p<0.01$) and Glasgow Coma Scale ($r_s = -0.15$, $p<0.01$) prior to intubation, along with the transport time to hospital ($r_s = 0.23$, $p<0.01$).

**Conclusion:** The PISA practices in the South African pre-hospital setting is comparable to international pre-hospital settings. The time to 1st PISA appears to be shorter in the SA setting. There is an increased number of interventions in the patients who received Rocuronium, which may indicate practitioners being mindful of wakeful paralysis. Practitioners also take the level of consciousness and blood pressure prior to intubation into account when administering PISA. Longer transport times attribute to patients receiving more PISA interventions.

Word count: 300

**Keywords:**
Endotracheal intubation, Emergency Medical Services, Post-intubation, Sedation and Analgesia

**African relevance**

- This article describes the current pre-hospital PISA practices in the South African setting to determine if improvement or policy change is needed.
- The patient sample is representative of the high burden of trauma in the South African pre-hospital setting.
- Optimal PISA practices early on may contribute to improvement on the long-term outcome of patients.
- South Africa has one of the more advanced pre-hospital EMS in Africa and this research can act as a guideline for pre-hospital policy and procedure development in other developing African countries.
- As in South Africa, other African countries experience similar challenges such as rural infrastructure and long pre-hospital transport times which provides external validity of this research to Africa as a whole.
A RETROSPECTIVE REVIEW OF POST-INTUBATION SEDATION AND ANALGESIA PRACTICES IN A SOUTH AFRICAN PRIVATE AMBULANCE SERVICE

Introduction

Endotracheal intubation (ETI) is a skill within the scope of practice of trained Advanced Life Support (ALS) practitioners in the South African pre-hospital setting. The ETI procedure can be facilitated by Rapid Sequence Intubation (RSI) or deep sedation (DS) intubation, and in some cases without medication (1,2). The ETI process and mechanical ventilation are uncomfortable and anxiety-provoking procedures for patients (3). Consequences of inappropriate or absent analgesia and sedation practices are numerous, particularly regarding the post-intubation period. Deeper sedation in the intubated patient, whether long term or in the early post-intubation period in the emergency setting has been associated with increased mortality, hospital length-of-stay (LOS), longer ventilation days and delirium (4,5). Conversely, inadequate sedation and analgesia during the post-intubation period and mechanical ventilation (especially when pharmacologically paralysed) may lead to increased catecholamine release and a multitude of undesirable consequences (6–8).

Medical facilities are often far apart in the rural regions of South Africa, which can lead to long pre-hospital transport times (4,5). Pharmacological agents and practice guidelines to ensure continued analgesia and sedation both prior to and in the post-intubation period should therefore be available to guide any medical practitioner who may perform this procedure.

After review of the literature, there appears to be no clear standard and guidelines for post-intubation sedation and analgesia (PISA) practices. As a result, sedation and analgesia of patients in the pre-hospital and aeromedical transport environment is usually left to the clinical judgment of the medical provider (11). Unfortunately, due to the unique challenges in the pre-hospital and aeromedical transport setting such as increased noise, significant vibration and jostling of the patient due to potentially rough terrain, lack of space and lighting, the protocols employed in the emergency centre (EC), where they have been validated, cannot simply be transferred to the pre-hospital environment, but needs to be adapted to this unique setting (5). In order to create appropriate guidelines for PISA, it is important to assess the current practice that is being employed in the pre-hospital setting. Very few studies have been published assessing these practices in the South African pre-hospital setting.
Thus, the primary aims of this study was to investigate if patients were routinely receiving sedation and analgesia post-intubation as well as the time frame and number of interventions of these medications. The secondary aims attempted to determine if there was an association between analgesia and sedation administration and paralytic use, and to describe the association, if any, of clinical parameters (systolic blood pressure, heart rate and Glasgow Coma Scale (GCS)) on the time to 1st sedation/analgesia administration as well as the mean number of sedation/analgesia interventions.

**Methodology**

A retrospective chart review was performed to describe the pre-hospital PISA practices in a South African private ambulance service.

**Study setting**

Patient report forms (PRF) from a single national private ambulance service were included for analysis in this study. This South African ambulance service treats and transports various patients in a primary as well as a transfer setting and consists of ground and aeromedical transport. A PRF must be completed for every patient treated by an employee of this company. These PRFs are serially numbered and electronically scanned by an external company and securely stored in an offsite facility to ensure that none of these reports are misplaced. The scanned electronic copies are available in a central billing system for record keeping and billing purposes. Various interventions performed on the patient are manually captured during the billing process. The system can therefore easily be searched for ETI interventions.

**Data collection**

All PRFs that had an intubation attempt logged during the period of 1 January 2017 to 31 December 2017 were captured and scrutinised for the inclusion and exclusion criteria. PRFs included for analysis were patients of all ages successfully intubated by an ALS practitioner in the pre-hospital setting. All intubation methods were included (RSI, DS and no medication intubation). PRFs not included for analysis were patients in cardiac arrest or who had died on scene or prior to hospital arrival. Patients that required more than two attempts at intubation were excluded for analysis of the objectives where time played a role, such as time to 1st PISA and correlation with vital sign changes.
This was because time of ETI was not consistently recorded. All the PRF’s were included for the determination of the proportion of patients who received PISA as well as the number of interventions.

Each PRF was scrutinised by a single data collector and variables were recorded according to pre-set criteria (see Appendix 3). The variables recorded included patient age, gender, mechanism of injury categorised into medical or trauma, intubation method, heart rate (HR), blood pressure and Glasgow Coma Scale (GCS) before and after intubation and after the 1st sedation and/or analgesia intervention, the medication types, dosages and administration times. The variables were recorded in a Microsoft Excel spreadsheet. The intubation time is not recorded on the PRFs and an estimation of intubation time had to be made according to the pre-set criteria. To verify accuracy, a 10% random sample was generated in Microsoft Excel and a 2nd data collector was tasked to record the data for this sample according to the same pre-set criteria. The 2nd data collector was trained on the process of recording the variables prior to the process. Recorded information was compared during a scheduled meeting and consensus regarding differences was reached by discussion. A 3rd independent party clarified two cases where consensus could not be reached. The sampled data was compared to the corresponding PRF information that was captured by the 1st data collector for inter-rater agreement.

**Data analysis**

The data in the Excel spreadsheet was coded to simplify statistical analysis. For missing vitals variables, the case was excluded pairwise during the analysis where these variables were required.

The data analysis was mostly descriptive in nature and presented as proportions and percentages, and mean times pertaining to 1st post-intubation intervention and number of post-intubation interventions. Analyses were done with the sample as a whole as well as separately according to intubation method (RSI, DS and no medication) and further between RSI with Succinylcholine (SCH) and Rocuronium (ROC) (or other long-acting neuromuscular blocking agent (NMBA)). An independent sample t test was performed to determine if there was a difference in the number of interventions between patients who had received ROC (either as a primary or as a secondary paralytic) and patients who did not (included patients were those who only received SCH or DS for induction. Patients who required no medication for intubation was excluded from this group).
An independent sample t test was also performed to determine if there were differences in the number of interventions between the RSI group and the DS group. Mann-Whitney U tests were run to determine the following:

- differences in time from estimated ETI to 1st PISA between RSI and DS
- differences in time from induction to 1st PISA between ROC and SCH as a primary
- differences between the mean times from 1st PISA to 2nd PISA and 2nd PISA to 3rd PISA between ROC and SCH and between RSI and DS.

The association between patient variables and patients receiving PISA was determined with odds ratio calculations. Spearman’s rank-order correlation coefficients were run to determine the relationships between the groups receiving PISA, number of PISA interventions and time from induction administration/estimated ETI (since not all patients had an induction agent administered) to 1st PISA and the remaining variables recorded.

A binomial logistic regression was performed to ascertain the predictive value of variables that had a statistically significant correlation in the above-mentioned groups on the likelihood of patients receiving PISA. Significance was two-tailed and determined at a value of p=0.05. The descriptive statistics were performed in the original Excel spreadsheet and the correlation and between-group comparisons were calculated using IBM SPSS statistics (12).

This study was a retrospective chart review and had no impact on the management of the patients in the report forms. Patient confidentiality was ensured by not recording any patient identifying information and anonymity was therefore guaranteed. Waiver of patient consent was requested and received by the University of Cape Town Human Research Ethics Committee. Ethics approval for this study was granted by the University of Cape Town Human Research Ethics Committee (HREC REF number 078/2020) as well as by the research committee of the private ambulance service from where the PRFs were derived (Ref number: Project 01/2020).
Results

There were 801 PRFs identified that had an intubation event logged according to the private ambulance service’s billing system over the study period. The PRFs were scrutinised and 364 were excluded according to the exclusion criteria (Fig. 1). Of the 437 that were included for analysis, 68 patients had multiple intubation attempts (included for primary objective analysis). Three hundred and sixty-nine PRFs were included for data capture and analysis of all of the objectives. There was a 95.2% inter-rater agreement between the data abstractors.

Eligible cases (n = 801)
- Duplicates removed (n = 3)
- Cardiac arrest cases (n = 240)
- Unsuccessful ETI/Self-extubation (n = 11)
- Pt not intubated/ LMA/ intubated in hospital/ tracheostomy (n = 79)
- Treated by other EMS service (n = 14)
- Critical data point missing/ Incomplete PRF (n = 17)

Eligible cases included for non-timeframe related objective analysis (n = 437)

Intubation timeline too wide/ >2 ETI attempts (n = 68)

Eligible cases included for timeline and vital sign correlation objective analysis (n = 369)

Figure 1B. Inclusion of cases

Of the 437 patients, 217 (49.6%) were intubated with RSI, (105 (24%) had ROC administered either as a primary or as a secondary NMBA and 112 (25.6%) had only received SCH during the intubation process), 162 (37.1%) were intubated with DS and 58 (13.3%) were intubated with no medication. Table 1 describes the demographic and basic distributions of the sample.
Table 1: Sample description (n = 437)

<table>
<thead>
<tr>
<th>Age distribution</th>
<th>Total</th>
<th>ROC</th>
<th>SCH</th>
<th>DS</th>
<th>No meds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child (&lt;18) n (%)</strong></td>
<td>39 (8.9)</td>
<td>6 (1.4)</td>
<td>12 (2.7)</td>
<td>18 (4.1)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td><strong>Mean age (range)</strong></td>
<td>8.6 (1-17)</td>
<td>6.2 (3-9)</td>
<td>8.7 (3-17)</td>
<td>9.3 (1-17)</td>
<td>9.7 (7-15)</td>
</tr>
<tr>
<td><strong>Adult (≥18) n (%)</strong></td>
<td>344 (78.7)</td>
<td>80 (18.3)</td>
<td>84 (19.2)</td>
<td>131 (30)</td>
<td>49 (11.2)</td>
</tr>
<tr>
<td><strong>Mean (range)</strong></td>
<td>43.5 (18-99)</td>
<td>40.2 (19-92)</td>
<td>39.7 (18-84)</td>
<td>46.8 (20-99)</td>
<td>46.6 (18-89)</td>
</tr>
<tr>
<td><strong>Unspecified n (%)</strong></td>
<td>54 (12.4)</td>
<td>19 (4.3)</td>
<td>16 (3.7)</td>
<td>13 (3)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td><strong>Total Age (±SD)</strong></td>
<td>40 (±20.4)</td>
<td>38 (±17.6)</td>
<td>36 (±18.5)</td>
<td>42 (±22.8)</td>
<td>44 (±19.6)</td>
</tr>
<tr>
<td><strong>Gender n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>315 (72)</td>
<td>82 (18.8)</td>
<td>85 (19.5)</td>
<td>107 (24.4)</td>
<td>41 (9.4)</td>
</tr>
<tr>
<td>Female</td>
<td>122 (28)</td>
<td>23 (5.2)</td>
<td>27 (6.2)</td>
<td>55 (12.6)</td>
<td>17 (3.9)</td>
</tr>
<tr>
<td><strong>Classification n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>118 (27)</td>
<td>15 (3.4)</td>
<td>24 (5.5)</td>
<td>57 (13.1)</td>
<td>22 (5.1)</td>
</tr>
<tr>
<td>Trauma</td>
<td>319 (73)</td>
<td>90 (20.6)</td>
<td>88 (20.1)</td>
<td>105 (24)</td>
<td>36 (8.2)</td>
</tr>
</tbody>
</table>

The odds of receiving PISA were found to be lower in females than in males (OR 0.62, 95% CI, 0.40 to 0.96 p=0.03) and the odds of receiving PISA higher in trauma patients than in medical patients (OR 1.42, 95% CI, 0.91 to 2.21 p=0.13). This was not statistically significant. There was a weak but statistically significant correlation between age of the patient and receiving PISA $r_s=0.11$ (p=0.03) with an increasing age more likely to receive PISA.

**Primary objectives**

More than two thirds of the patents in the total sample had received some type of PISA intervention (Fig. 2). Patients who had received ROC during the RSI procedure (either as a primary or as a secondary NMBA) had a higher likelihood of receiving PISA than patients who had only received SCH during the RSI procedure (OR 2.32 (95% CI, 0.96 to 5.60 p=0.06)). This was not statistically significant.
Patients who were intubated with RSI overall were also more likely to receive PISA over patients who were intubated with DS (OR 5.45 (95% CI, 3.26 to 9.12 p<0.01)). The odds ratio of receiving PISA between RSI and no medication intubation was 16.33 (95% CI, 8.18 to 32.58 p<0.01) and between DS and no medication was 3.00 (95% CI, 1.58 to 5.67 p<0.01).

The time from estimated time of intubation to 1st PISA was fairly similar between the groups, ranging from 9 to 12 minutes (Table 2). The time from induction administration to 1st PISA ranged from 10 to 17 minutes, with the DS group being the most delayed to PISA. Median time from estimated ETI to 1st PISA between RSI (8 min) and DS (10 min) was not statistically significantly different, p=0.08. Median time to PISA between RSI with ROC (10 min) and RSI with SCH (10 min) was not statistically significantly different, p=0.85.

The times from the 1st PISA to the 2nd PISA for the groups ranged from 8.8 minutes to 17.8 minutes. Median time from 1st to 2nd PISA between RSI with ROC (15 min) and RSI with SCH (10.5 min), was statistically significantly longer, p<0.01. The median time from 1st to 2nd PISA between RSI (14 min) and DS (11.5 min), was not statistically significantly different, p = 0.64 and neither were there significant differences between RSI with ROC vs DS and RSI with SCH vs DS. The times from 2nd to the 3rd PISA ranged from 9.7 minutes to 17.3 minutes. There were no statistically significant differences in the medians between the groups.
### Table 2: Time (in minutes) to 1st and subsequent PISA

<table>
<thead>
<tr>
<th>Time from induction to 1st PISA in minutes</th>
<th>Total (n=284)</th>
<th>ROC (n=97)</th>
<th>SCH (n=94)</th>
<th>DS (n=92)</th>
<th>No med (from estimated ETI time n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD)</td>
<td>12.9 (±8.3)</td>
<td>10.4 (±6.8)</td>
<td>10.9 (±5.9)</td>
<td>17.4 (±9.9)</td>
<td>11 (±7.8)</td>
</tr>
<tr>
<td>Median</td>
<td>10.5</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from estimated ETI to 1st PISA</th>
<th>Total (n=262)</th>
<th>ROC (n=91)</th>
<th>SCH (n=84)</th>
<th>DS (n=73)</th>
<th>No med (from estimated ETI time n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD)</td>
<td>10.1 (±7.4)</td>
<td>9 (±6.9)</td>
<td>9.5 (±5.6)</td>
<td>12 (±9.2)</td>
<td>11 (±7.8)</td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from 1st PISA to 2nd PISA in minutes</th>
<th>Total (n=138)</th>
<th>ROC * (n=59)</th>
<th>SCH (n=50)</th>
<th>DS (n=28)</th>
<th>No medication (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD)</td>
<td>13.9 (±7.4)</td>
<td>17.8 (±10.4)</td>
<td>11.3 (±5.5)</td>
<td>15.4 (±11.6)</td>
<td>8.8 (±2.9)</td>
</tr>
<tr>
<td>Median</td>
<td>12.5</td>
<td>15</td>
<td>10.5</td>
<td>11.5</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from 2nd PISA to 3rd PISA</th>
<th>Total (n=64)</th>
<th>ROC (n=28)</th>
<th>SCH (n=26)</th>
<th>DS (n=7)</th>
<th>No medication (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD)</td>
<td>15.2 (±9.2)</td>
<td>16.8 (±8.5)</td>
<td>13.5 (±10)</td>
<td>17.3 (±9.6)</td>
<td>9.7 (±5.5)</td>
</tr>
<tr>
<td>Median</td>
<td>12.5</td>
<td>15</td>
<td>11.5</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

* - 3 extreme outliers removed (2 of the cases were removed since the rocuronium was administered as a secondary long-acting NMBA more than 90 minutes after the intubation process. Sedation was concomitantly administered, therefore the time between the 1st PISA and the 2nd PISA is unreasonably long. The third case had an extremely long transport time, accounting for the delays between the PISA interventions, which unreasonably skewed the data).

**Secondary objectives**

There was a statistically significant difference (p<0.01) between the mean number of PISA interventions in the ROC group and the mean interventions in the non-ROC group (Table 3). The ROC group received 0.72 (95% CI, 0.47-0.97) more interventions than in the non-ROC group. There was also a statistically significant difference (p<0.01) between the RSI and DS groups, with the RSI group receiving 0.95 (95% CL, 0.737-1.169) more interventions than the DS group.
Table 3: Total number of interventions

<table>
<thead>
<tr>
<th></th>
<th>Total (n=301)*</th>
<th>ROC (n=96)*</th>
<th>SCH (n=94)</th>
<th>DS (n=93)</th>
<th>No med (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD)</td>
<td>1.8 (±1)</td>
<td>2 (±1)</td>
<td>1.9 (±1)</td>
<td>1.4 (±0.7)</td>
<td>1.6 (±1.3)</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* - 1 extreme outlier was removed from the sample where a patient received 8 interventions during the time from intubation to handover at hospital. The range for the remainder of the patients were between 0 and 5 interventions. This data point caused significant deviations in the sample and was therefore removed.

Table 4 depicts the statistically significant correlations between the variables and PISA and number of interventions. The logistic regression model was statistically significant, p < 0.01. Of the seven predictor variables only three were statistically significant: time from induction to destination, MAP prior to intubation and ETI method. An increase in the MAP had a marginally increased likelihood of receiving PISA (OR 1.01 (95% CI, 1.00 – 1.02, p=0.03)). Patients intubated with RSI had 5.8 times higher odds of receiving PISA (95% CI, 3.26 – 9.12, p=0.01) than those intubated with DS and increased time to destination had a marginally higher likelihood of receiving PISA (OR 1.03 (95% CI, 1.01 – 1.05, p<0.01)).
Table 4: Statistically significant correlations

<table>
<thead>
<tr>
<th>Correlation variable</th>
<th>Correlation variable</th>
<th>Subgroup</th>
<th>Spearman's correlation coefficient</th>
<th>Sig. (2-tailed) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of interventions</td>
<td>Map before intubation</td>
<td>Full sample</td>
<td>$r_s = 0.17$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>RSI group</td>
<td></td>
<td>$r_s = 0.25$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>GCS prior to intubation</td>
<td>Full sample</td>
<td>$r_s = -0.15$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>RSI group</td>
<td></td>
<td>$r_s = -0.25$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>Difference in MAP from before intubation to after intervention</td>
<td>Full sample</td>
<td>$r_s = -0.19$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>RSI group</td>
<td></td>
<td>$r_s = -0.27$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>Time from induction to time at destination</td>
<td>Full sample</td>
<td>$r_s = 0.23$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>RSI group</td>
<td></td>
<td>$r_s = 0.29$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>DS group</td>
<td></td>
<td>$r_s = 0.28$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>Received premed</td>
<td>Full sample</td>
<td>$r_s = 0.13$</td>
<td>$p=0.01$</td>
</tr>
<tr>
<td>Received PISA</td>
<td>GCS prior to intubation</td>
<td>Full sample</td>
<td>$r_s = -0.15$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>RSI group</td>
<td></td>
<td>$r_s = -0.15$</td>
<td>$p=0.04$</td>
</tr>
<tr>
<td></td>
<td>Difference in MAP from before intubation to after intervention</td>
<td>DS group</td>
<td>$r_s = -0.24$</td>
<td>$p=0.01$</td>
</tr>
<tr>
<td></td>
<td>Received premed</td>
<td>Full sample</td>
<td>$r_s = 0.14$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>Time from induction to time at destination</td>
<td>Full sample</td>
<td>$r_s = 0.18$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>RSI group</td>
<td></td>
<td>$r_s = 0.18$</td>
<td>$p=0.01$</td>
</tr>
<tr>
<td></td>
<td>DS group</td>
<td></td>
<td>$r_s = 0.25$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>Difference in HR from before intubation to after intervention</td>
<td>RSI group</td>
<td>$r_s = -0.23$</td>
<td>$p&lt;0.01$</td>
</tr>
</tbody>
</table>

Additional analysis

Additional analysis was performed on the PISA interventions. These interventions ranged from Morphine, Midazolam, Ketamine, Diazepam, Lorazepam, Etomidate or various combinations of these. The majority of the interventions were Morphine, Midazolam or a combination thereof (76.6% of the patients who had received some type of PISA).
Basic descriptive statistics were performed on this majority groups of PISA interventions since these are the PISA agents recommended by local guidelines (13). The other PISA interventions lacked a clear protocol and there was no structure discernible from its administration. The average dose of Morphine (±SD) when administered as a singular agent for the 1st intervention post ETI was 4.1mg (±1.1), as the 2nd intervention 4.6mg (±0.5) and as the 3rd intervention 3.4mg (±1.2). The results for Midazolam as a singular agent post-ETI was 4.4mg (±2.5), 4mg (±2.2) and 3.6mg (±1.1) for 1st, 2nd and 3rd intervention respectively. For a Morphine/Midazolam combination, the results were 3.6mg (±1.4)/3.6mg (±1.3) for 1st intervention, 3.4mg (±1.2)/3.2mg (±1.2) for 2nd intervention and 3.2mg (±1)/3mg (±1) for the 3rd intervention.

Discussion

This study described the PISA practices in the South African pre-hospital setting. Up to 75% of patients intubated with the help of an induction agent in the pre-hospital environment received some type of PISA by pre-hospital providers. This figure is similar to that in the 2017 study by Stein in the same setting where it was found that 72% of patients received Morphine and 63% received Midazolam (10). However, there is still a quarter of the patients who had required an induction agent prior to intubation that did not receive any PISA.

The demographic descriptors of the patients were similar to other studies done in the South African pre-hospital setting with the predominant population being young males with trauma (10,14,15). Interestingly, males were more likely to receive PISA than females, which may be due to their physical ability to be more disruptive and harder to restrain than females or their illness or injury requiring it. The reason remains unclear though.

Historically, a common indication for the administration of sedation was purported to be patient movement, a sign that is masked by NMBAs. As such, patients at risk of awake paralysis is twice as high in patients who received a NMBA (16). Due to the false sense of sedation in a paralysed, immobile patient, long acting NMBA administration have been associated with delays in initiation, as well as lower doses of post-intubation sedation (7,17). The current study found that the time to the 1st intervention after intubation was administered at similar times between the different methods of intubation. The average number of interventions were higher in the patients who had received ROC, possibly alluding to the mindfulness of the practitioners that patients who had received ROC will not be able to show any indication of wakefulness. This finding was similar to other studies (16,17).
There was however a statistically significant difference between the 1st and 2nd PISA administrations between the ROC and SCH groups. This may be due to the patients in the SCH subgroup being able to move and alert the practitioner to their wakefulness whereas the patients in the ROC group was not. The 1st PISA administration may therefore be due to mindfulness of guidelines, whereas the 2nd dose may be due to patient factors. The delay may be caused by the practitioner being busy with other life-saving interventions and only administering the 2nd dose later, whereas if the patient did not receive a long-acting NMBA, they will start to move sooner, encouraging the practitioner to intervene.

Despite this delay, the time frame noted was still an improvement when compared to a 2013 study done by Watt et al, where it was found that the mean time to post-intubation sedation was 27 minutes after RSI with long-acting ROC, which left these patients without sedation for approximately 20 minutes when Etomidate was used as an induction agent (18). Similar results were found in a study by Johnson et al in 2015, with time to post-intubation sedation being 34 minutes in the ROC group compared to 16 minutes in the group who received Succinylcholine (6). This time was considerably shorter in an EC study done by Kilber et al in 2018 that found that the average time to post-intubation sedation was 8 minutes after RSI with Rocuronium (1). From these studies, there appears to be an improvement in time to PISA over the years. This may be due to increased research into current practice or updated protocols with regards to PISA.

Practitioners may be more cognisant of patients' potential awareness during pharmacological paralysis and therefore administering more PISA, or that the patients were not settling from the PISA and was therefore given the long-acting NMBA. A retrospective cohort EC study done by Chong et al in 2014 assessed sedation prior to and after administration of a long-acting NMBA and found that patients who had received ROC as a primary NMBA, were twice as likely to go without sedation than patients who received it as a secondary agent for continued paralysis (7). This was not found in the current study where there was no significant difference in receiving PISA or the number of interventions between patients who had received ROC as a primary compared to those who had received it as a secondary agent. Furthermore, patients who had received ROC had generally received significantly more PISA interventions than those who did not receive a long-acting NMBA. This was similar to the US pre-hospital retrospective study in 2019 by Billups et al, who found that there was also no difference between the number of sedative doses administered between the two groups (17). This may once again speak to the practitioners being cognisant of awake paralysis in patients who are pharmacologically paralysed.
The difference may also allude to the possibility of patients being too deeply sedated in this setting since the patients in the SCH group did not require as many interventions as was administered in the ROC group. The practitioners may therefore have been overly cautious of awake paralysis.

This study found that there was a statistically significant correlation between the MAP before intubation and receiving PISA, with a higher MAP resulting in a higher likelihood of receiving PISA. An increase in the MAP from before intubation to after the interventions was also a positive predictor of patients receiving more interventions. These correlations were weak though and the clinical significance may be questionable. It does however indicate that practitioners may take the blood pressure into account before administrating PISA, which is a similar finding to other studies. Berg et al found that there was a 2% increase in receiving post-intubation sedation for every 1mmHg increase in pre-intubation systolic blood pressure (19). This speaks to clinicians either being wary of causing hypotension when it comes to sedation or they interpret an increase in blood pressure as a sympathetic stress response which may require more sedation. A higher pre-ETI GCS weakly correlated to patients receiving PISA. This may indicate that either the practitioners were keeping the patient's wakefulness prior to intubation in mind and administering PISA accordingly, or that the patients were more responsive post-intubation and therefore required more sedation/analgesia after intubation. This trend was seen in the analysis of the full sample and the RSI subgroup but not the DS and no medication subgroups. A possible explanation for this trend may be that the DS group administered induction medications that had a longer duration of action than those administered in the RSI group and less PISA interventions were therefore needed.

The strongest correlation for receiving PISA and the number of interventions was seen with the transport time to hospital, with a longer transport time resulting in more interventions as well as a higher likelihood of receiving an intervention. This was to be expected since the patients would require more interventions as the transport time increase and they intermittently woke up. A short transport time may therefore account for some of the patients who did not receive any PISA intervention.
Additional analysis was performed with regards to the type and dose of PISA interventions. These analyses were limited to the recommended post-intubation interventions in the Emergency Medicine Society of South Africa (EMSSA) RSI practice guidelines which is the administration of Morphine, Midazolam or a combination of these. It was interesting to note that the average dose ranged between 3.5 and 4mg of Morphine, Midazolam or a combination of both. This is essentially double the recommended dose in the guideline which states 1-2mg every 10 minutes as required (13). These differences may be due to patients requiring higher dosages and more PISA interventions in practice than what is recommended in the guidelines, or it may indicate that patients are too deeply sedated in the pre-hospital environment, which has been indicated as a problem in previous research (5,20,21). It may also be due to the possibility that the recommendations are based on practice in hospital and not on practice in the chaotic pre-hospital environment where vibration and noise may increase the requirement for sedation and analgesia (5). Either way, these guidelines may need to be reviewed.

Limitations

Since this study was a retrospective chart review, it was subjected to the common limitations of this type of study. This included the possibility of inaccurate or missing information in the documentation and poor external validity since the study population was derived from a single private company with their own policies and procedures. Another limitation of the study was the fact that intubation times were not recorded on the patient forms. In order to determine time from intubation to 1st PISA, an estimate of intubation time had to be made. The criteria that this time was based on was however applied to all of the subgroups. Time from induction to 1st PISA was also calculated but was not feasible for comparison between some of the subgroups since this led to a prolonged time to 1st PISA in the DS group.

This was due to the induction agents in this group having a longer onset of action than those in the RSI groups. Analysis where this time frame was used was isolated to the RSI group between ROC and SCH subgroups. There was also no induction administered in the no medication groups which would also make the time from induction to 1st PISA in this group problematic. There was a wide variety of post-intubation medications administered in the population. This made the analysis of these interventions difficult to compare. These medications had different durations of action which also fluctuate based on the dosages administered. This may have had an effect of the timings of PISA administration as well as the number of interventions.
Conclusion

The post-intubation sedation/analgesia practices in the South African pre-hospital setting appears similar to practices in international pre-hospital settings. There was still approximately a quarter of patients who required some type of induction during the intubation process, who did not receive any PISA. This may possibly be due to administration not being required i.e., minimal movement or signs of agitation during transport, patients being obtunded prior to intubation, use of a long-acting NMBA (although this number was very small at only 8 patients) or the time to hospital was short enough that they reached their destination prior to additional PISA being required.

The time to 1st PISA was shorter and there was an increased number of interventions in patients who had received ROC. The practitioners therefore appear mindful of wakeful paralysis. The dosage of PISA was considerably higher than the recommended guidelines for this setting, which may result in the patients being too deeply sedated or that the patients need the higher levels of sedation in this particular setting. Either way, the guidelines may have to be reviewed and tailored to this unique setting.

Current guidelines recommend early administration of post intubation sedation, before the induction agent wears off. The authors recommend that the administration of PISA be protocolised in the South African pre-hospital setting and that the administration of PISA not be left up to the discretion of the practitioner. It is further advised that a prophylactic loading dose of an opioid be administered immediately after successful intubation and additional sedation titrated after this. The administration of PISA should be independent from the method of intubation. EGD PISA should be implemented into the RSI or intubation protocol as a whole with dosage recommendations. Protocolising post-intubation sedation is challenging since every patient will have an individual need and goal for the sedation. If it is simply to prevent agitation, self harm and self-extubation then a lighter level of sedation can be maintained. However, if it is to obtain a clinical goal such as ventilator control and synchrony, then a deeper sedation level might be required.
Dissemination of results

The results of the study, including the full article was made available to the private ambulance company from where the patient report forms originated. The deidentified raw data will be made available upon request.

Author’s contribution

Authors contributed as follows to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content:

JMDK contributed 50%; WS 25%; and CB contributed 25%.

All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors declared no conflict of interest.
References


10. Stein C. Student paramedic rapid sequence intubation in Johannesburg, South Africa:


12. IBM SPSS Statistics Software subscription.


PART C: APPENDICES
Appendix 1: Instructions for authors

The journal selected for publication of this study was the African Journal of Emergency Medicine since the study pertains to the African pre-hospital environment. The recommendations made is also based on the practices in the South African and African setting.

The manuscript was completed according to the Guide for Authors which can be found at the following link:

www.elsevier.com/locate/afjem
### Appendix 2: Data capture sheet

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age/ (Adult or child)</th>
<th>Gender</th>
<th>Trauma/medical</th>
<th>ETI method</th>
<th>Received PIS</th>
<th>Received Roc/sux only/NA</th>
<th>Time of vitals before ETI</th>
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<td></td>
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<tr>
<td>SBP before ETI</td>
<td>DBP before ETI</td>
<td>MAP before ETI</td>
<td>HR before ETI</td>
<td>GCS before ETI</td>
<td>Pre med</td>
<td>Premed time</td>
<td>Dose</td>
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<tr>
<td>Time of induction adm</td>
<td>Induction agent</td>
<td>Dose</td>
<td>Estimated time of ETI</td>
<td>Time of vitals after ETI</td>
<td>SBP after ETI</td>
<td>DBP after ETI</td>
<td>MAP after ETI</td>
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<tr>
<td>HR after ETI</td>
<td>Time of first post ETI sedation</td>
<td>Intervention</td>
<td>Dose</td>
<td>Time of intervention 2</td>
<td>Intervention</td>
<td>Dose</td>
<td>Time of intervention 3</td>
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</tr>
<tr>
<td>Intervention</td>
<td>Dose</td>
<td>Number of interventions</td>
<td>Long acting paralytic time</td>
<td>Post LAP sedation time</td>
<td>Post LAP sedation time 2</td>
<td>Time of vitals after intervention/last vitals if no intervention</td>
<td>SBP after intervention</td>
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<tr>
<td>DBP after intervention</td>
<td>MAP after intervention</td>
<td>HR after intervention</td>
<td>At destination</td>
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</tbody>
</table>
## Appendix 3: Data capture criteria and variable definitions

<table>
<thead>
<tr>
<th>General</th>
<th>Reasoning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Justification for research methodology</strong></td>
<td>A retrospective chart review was chosen to conduct this study to determine current practice in the field without introducing potential bias as is sometimes the case with prospective studies. There are also more ethical considerations with a prospective study than with retrospective studies, especially with emergent cases.</td>
</tr>
<tr>
<td><strong>Reasoning for including multiple attempts at intubation:</strong></td>
<td>Originally, the reason for only including first pass success intubations was to have a relatively accurate intubation time. In this way, it can be deducted whether patients receive timely post intubation sedation. However, from what could be seen from the data, an accurate intubation time can only be deducted from first pass success RSIs. If deep sedation was used, then there must still be time allowed for the sedation to take effect, even if the intubation is successful on first attempt, the exact time is not obtainable. The same goes for intubations where no medications were used. The intubation time was estimated in these cases as the halfway time between the sedation administration and the next vital sign time where the patient was intubated, or between the two vital sign times where the patient was not and then was intubated. Criteria had to be set up as to when a patient was deemed to be intubated. These criteria were as follows:</td>
</tr>
<tr>
<td><strong>Intubation is determined by either of the following:</strong></td>
<td>- Change in GCS from a whole number to 2T where the verbal component is changed to a T for tubed (the majority of the report forms had this indication, however for those who did not, further criteria was established)</td>
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<td>- If the verbal component is not changed then it will be when the GCS is recorded as 3 after the induction agent administration (unable to use this method if the patient’s GCS was originally 3)</td>
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<td>- The documentation of an EtCO2 reading</td>
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<td></td>
<td>- The documentation of ventilation settings</td>
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<td></td>
<td>- If the time of intubation is documented by the practitioner</td>
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<td></td>
<td>- If none of these were present to indicate when the patient was intubated then no reliable intubation time estimate could be determined and the PRF was only used for limited analysis</td>
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<tr>
<td></td>
<td>- All of the above was subject to the vital sign times, from which the estimates were made, were 10 minutes or less apart. Any longer would have created too broad of a time frame. For example, time of vitals where patient was not intubated 12:35 and time of vitals where patient was intubated 12:45, intubation estimate would be 12:40.</td>
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<tr>
<td></td>
<td>- If the induction dose was administered within these 10 minutes, then the hallway mark between the induction time and next vital sign time, where the patient was intubated was taken. For example, vital sign time where patient was not intubated 12:35, vital sign where patient was intubated 12:45, midazolam administered at 12:39, then intubation time would have been estimated at 12:42. If the hallway mark was an uneven number, then it was rounded up to the next full minute.</td>
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<tr>
<td></td>
<td>- If the patient had received RSI and it was a first pass success, then the intubation time was taken as 1 minute after the paralytic dose administration time.</td>
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</table>
Reasons why multiple attempts were included in the sample for data capture and analysis of all objectives:

- As can be seen from the criteria above, estimates about intubation times had to be made due to the nature of the documentation
- If a time estimation was made for a first pass success, then there was no reason to not estimate for two attempts
- Therefore, if the same criteria were applied to multiple attempts at intubation, then a large portion of these cases could be included in the data capture sample

Additional criteria that will be applied for multiple intubation attempts will be as follows:

- Only up to 2 attempts at intubation were included for full analysis. Additional attempts may have increased the stimulation on the vagus nerve and started affecting the vital signs and may have affected the correlation between post intubation sedation and vital signs (1)
- In the case of RSI, if it was not first pass success then the intubation time was estimated as the hallway time between the paralytic administration time and the time of the next vital sign where the patient was intubated. If this time frame was wider than 10 minutes then the PRF was discarded from full data collection and analysis.
- All of the other criteria for first pass success was employed for no medication and deep sedation intubations.


Data capture point

<table>
<thead>
<tr>
<th>Data capture criteria and variable definitions</th>
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<tbody>
<tr>
<td>Patient number</td>
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<tr>
<td>Age of patient</td>
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<tr>
<td>Gender</td>
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<td>Trauma or medical</td>
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<td>Intubation method</td>
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<td></td>
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<tr>
<td>Received PIS (post intubation sedation)</td>
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</tbody>
</table>
### Time of vitals before intubation
- Vitals before induction agent is administered,
- If there are more than one vital sign set before intubation then the vital sign set closest to the intubation time is preferable, unless a large amount of pre-medication was administered and the patient is significantly sedated. Then the vital sign set before this, is preferred.
- If there is no blood pressure recorded or blood pressure was indicated to be unrecordable, just leave blank
- If there is only a systolic blood pressure, record only the systolic blood pressure and leave the diastolic blank

### Premedication
- Can include morphine, midazolam, lorazepam or diazepam (usually in the case of seizures), ketamine
- Premedication is indicated as the following
  - A smaller dose sedation or analgesia before induction in the case of RSI
  - If the intubation time can be estimated based on the pre-set criteria, the time that the induction agent was administered can be deducted. Any sedation and analgesia before this time will be considered as pre-medication
  - If there was more than one dose administered, record the dose that was administered closest to the induction administration
  - If more than one medication was administered over the same time, write both or all of the medications (eg. Morphine and midazolam, or midazolam and ketamine etc)

### Premedication time
- Time that the premedication was administered

### Premedication dose
- Write the doses in sequence if there were more than one medication at the same time administered

### Time of induction administration
- Administration of the paralytic agent during RSI
- Administration of the largest dose of sedation and or analgesia (this must coincide with the time of intubation, as estimated by the above-mentioned criteria)
- If no medication is used for intubation, leave blank
- Xylocaine is allowed as an induction agent

### Induction agent
- May include etomidate, ketamine, midazolam alone or in combination with morphine or morphine alone.
- If more than one medication is administered 2 min or less apart, then it can be assumed that they are both induction medications, if they are administered more than 3 minutes apart, the one is either a premedication or a post intubation sedation.
- The distinction must be made based on the estimated time of intubation as deducted from the vital sign times.
- If this cannot be deducted accurately, then the largest dose is considered the induction agent.
- If the dosages are the same, then the sedation agent will be considered as the induction agent (eg midazolam)

### Dose of induction
- Write the doses in sequence if there were more than one medication at the same time administered

### Estimated time of intubation
- An estimate of intubation time is made. This is the half way time between the time of vitals before and after intubation (as indicated by the criteria mentioned above).
| **Time of vitals after intubation** | • The time of the first vitals after intubation  
• This will be indicated by the criteria above.  
• If the first vital sign set after intubation time falls within 2 minutes of deep sedation administration, then the next vital sign set should be recorded |
| **Time of intervention** | • Time of first post intubation sedation and or analgesia  
• This can be midazolam, morphine, ketamine, diazepam, lorazepam or a  
  combination of these  
• If more than one agent is administered within 2 minutes of each other, they can be considered as being administered together. The earliest time will be recorded. |
| **Intervention** | • Type of agent, write all if there was more than one |
| **Dose** | • How many times sedation, analgesia or both were administered after intubation  
• If more than one agent is administered at the same time, this is classified as one intervention |
| **Number of interventions** | • Only for RSI cases  
• Must be recorded if a long acting paralytic (rocuronium) was used for the primary paralytic as well as secondary paralytic |
| **Long acting paralytic administration time** | • Time of sedation and or analgesia administration post long acting paralytic administration  
• This can be the same time as when the LAP was administered  
• It can also be before the LAP (if this LAP was NOT used as the primary paralytic for intubation) was administered if this time is less than 10 minutes  
• The subsequent sedation times is then also recorded if applicable |
| **Post long acting paralytic (LAP) sedation time** | • The time of first vitals after the first post intubation sedation and or analgesia was administered.  
• If the time of the vitals coincides with the time of the sedation administration, then the next vital sign set should be taken  
• If there are no subsequent vital signs, then this can be left blank  
• If no medication was used for intubation or if no post intubation sedation is administered then the last set of vital signs are recorded before handover. |
| **At destination time** | • Can be obtained from the first page of the PRF  
• If not at destination time is recorded, the handover time is recorded. If the patient is handed over to the heli, then depart scene time can be recorded. |
Appendix 4 Research proposal

A RETROSPECTIVE REVIEW OF POST-INTUBATION SEDATION AND ANALGESIA PRACTICES IN A SOUTH AFRICAN PRIVATE AMBULANCE SERVICE

Student: Joalda Marthine de Kock
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University of Cape Town
Student number: DKCJOA002
Email: joalda.dekock@gmail.com

Supervisors: Dr Willem Stassen
BTEMC, MPhil EM, PhD
Division of Emergency Medicine
University of Cape Town

Chloe Buma
BTEMC, MPhil EM
This study is in partial fulfilment of the MPhil in Emergency Medical Care degree

Declaration:

I, Joalda Marthine de Kock, 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 a degree.

Signature: Joalda Marthine de Kock Date: 29/10/2019
Plagiarism declaration

Division of Emergency Medicine
Department of Surgery
University of Cape Town
2015

Declaration
(To be submitted with each assignment)

Name: JM de Kock
Assignment: Research Proposal

Plagiarism Declaration:
1. I know that plagiarism is a serious form of academic dishonesty.
2. I have read the document about avoiding plagiarism, am familiar with its contents and have avoided all forms of plagiarism mentioned there.
3. Where I have used the words of others, I have indicated this by the use of quotation marks.
4. I have referenced all quotations and properly acknowledged other ideas borrowed from others.
5. I have not and shall not allow others to plagiarise my work.
6. I declare that this is my own work, and has not been previously submitted for marking purposes at any institution of higher learning, and has been properly referenced if previously published.¹
7. I am submitting the document in a format so as to allow Turnitin to check my work.
8. I am aware that I had a chance to see the Turnitin report and can resubmit an improved document if still within the allowed submission timeframe.

Signature Removed

Signature
Date: 23/10/2019

¹ Clarification added by the Division of Emergency Medicine, UCT.
Summary

Endotracheal intubation, whether facilitated by rapid sequence intubation medication or procedural sedation, is performed regularly in critically ill or injured patients in the pre-hospital setting of South Africa. Being intubated is an uncomfortable and painful experience. Since pain and anxiety may increase sympathetic response which can be detrimental for numerous medical and traumatic conditions, patients need to be appropriately sedated and analgised post-intubation.

Pre-hospital practitioners work in a human resource limited setting where they are often alone in the back of the ambulance with the patient (as opposed to the in-hospital setting where multiple practitioners care for the patient). They thus have multiple tasks to perform, often all at once. It is therefore possible for them to neglect administering sedation and analgesia to the patient post-intubation. This may especially be the case when a patient has received a long-acting neuromuscular blocking agent and is therefore not moving, thereby not giving any indication of awareness as might be the case with patients that were intubated with simple procedural sedation. Even in procedural sedation cases, it is not ideal for a patient to alert the practitioners as to their wakefulness before additional analgesia and sedation is administered.

Very few studies have been published assessing the practices of post-intubation sedation and analgesia in the South African pre-hospital setting. This study aims to investigate if patients are routinely receiving sedation and analgesia post-intubation.

A descriptive analysis of post-intubation sedation and analgesia practices will be conducted on patient report forms from a private ambulance company in South Africa over a one-year period. The analysis will examine whether analgo-sedation was administered, the time-frame in which it was administered and any potential correlation with heart rate and blood pressure changes pre- and post-administration. The difference in analgo-sedation administration time frames between the various intubation medications will also be analysed. From this analysis, current sedation and analgesia practices can be described in the South African pre-hospital setting. Following which, comparisons can be made between our results and the existing best practice recommendations in the literature, and potential improvements implemented. An ethical consideration that will be taken into account is patient confidentiality, since the patient medical records usually contain the personal details of each patient. This will be mitigated since the medical records will be de-identified prior to data extraction.
Background

South Africa is classified as a middle-income country with a significantly higher burden of trauma morbidity and mortality than the global average (1). Pre-hospital emergency medical services (EMS) have limited capacity and are frequently over-burdened (2,3). Medical facilities are often far apart, especially in the rural regions. These resource constraints and poor infrastructure often lead to long pre-hospital transport times in South Africa. The South African government recommends that there be at least 2 medical personnel on an ambulance unit and one ALS on a response vehicle (4). This will result in one person operating the vehicle and the other treating the patient. If the ALS accompanies the patient to hospital then the response vehicle needs to be operated as well. This leaves only one individual caring for a critical patient at a time.

Emergency pre-hospital intubation performed by trained advanced life support (ALS) practitioners is a recognized skill in the South African pre-hospital setting (2). Intubation can be facilitated by procedural sedation (usually involving morphine and midazolam) as well as rapid sequence intubation (RSI). Rapid sequence intubation is the near simultaneous administration of a potent short-acting induction agent and neuromuscular blocking agent (5). This is to facilitate the placement of an endotracheal tube into the trachea. Induction agents available in the South African pre-hospital setting include etomidate and ketamine and the neuromuscular blocking agents (NMBA) include the short-acting succinylcholine and the intermediate- to long-acting rocuronium and vecuronium (2,6). Procedural sedation medications to facilitate intubation include morphine and midazolam. These medications have several adverse effects associated with them, one of which is hypotension, which is detrimental in most ill or injured patients (7,8).

Endotracheal intubation and mechanical ventilation are extremely uncomfortable and anxiety-provoking procedures (9). Signs and symptoms of pain and anxiety are therefore common in mechanically ventilated patients (9,10). Inadequate sedation and analgesia during intubation and mechanical ventilation (especially when pharmacologically paralysed) may lead to increased catecholamine release and a multitude of undesirable effects including tachycardia, hypertension, anxiety, psychological trauma, increased coagulability, myocardial infarction and self-extubation (when the paralysis wears off without adequate sedation) (11–13). It is therefore important to continue sedation and analgesia when a long-acting agent is used (11).
During the procedure of RSI, the induction agent has a short duration of action and if administered with succinylcholine (which also has a short duration of action), will wear off approximately simultaneously (5). However, if the induction agent is administered with a long-acting paralytic such as rocuronium, the patient may be pharmacologically paralysed with inadequate sedation in the post-intubation period (5).

During transport of the intubated patient, there is usually only one practitioner caring for the patient, the other medics will be operating the vehicles (one for the ambulance and one for the response vehicle). The practitioner in the back of the ambulance will have multiple tasks to perform, often all at once. This may lead to the treating practitioner being distracted by managing other interventions during the post-intubation period or losing track of the time it takes the induction agent to wear off (12). It is therefore possible for them to neglect administering sedation and analgesia to the patient post-intubation. This may especially be the case when a patient has received a long-acting neuromuscular blocking agent and is therefore not moving, thereby not giving any indication of awareness as might be the case with patients that were intubated with procedural sedation (11). Even in the procedural sedation cases, it is not ideal for a patient to alert the practitioners as to their wakefulness before additional analgesia and sedation is administered.

Some other considerations that may influence the administration of post-intubation analgesia and sedation include the practitioner’s fear of adverse events such as hypotension, inability of the practitioner to gauge the patient’s sedation level due to the action of a long-acting paralytic and simple negligence due to shortage of human resources (9,13,14).

It is unacceptable, but unfortunately often the case that the movement of a patient is the only clinical indicator to alert the practitioner to administer additional sedation and analgesia (11). Research has shown that patients receiving short acting agents are more likely to receive additional sedation than those receiving long-acting agents, leading to the conclusion that the late reminder of patient movement is the indication for sedation administration (5,11,15). All of these events may exacerbate the existing medical or traumatic condition for which the airway management strategy was employed (11). It is classified as a medical error or adverse event if a patient is pharmacologically paralysed without sedation and analgesia (12).
Patients have better outcomes with early analgesia and sedation administration post-intubation, however this practice is poorly defined (10,13). Conversely, procedural sedation in the early post-intubation period in the intensive care unit (ICU) has been found to increase mortality (10). In the ICU, targeted sedation practices are employed based on various sedation scores such as the Ramsey sedation scale or the Richmond Agitation Sedation Scale (RASS) (10,16). This is unfortunately inaccurate when a patient is paralysed since most of these scores are based on the ability to arouse the patient (10,16). Other protocols for targeted sedation practices can possibly be defined and employed in the pre-hospital setting.

Very few studies exist regarding the post-intubation sedation practices in the prehospital and Emergency Centre (EC) environment (10). Of those that have been done, it is reported that up to 50% of patients do not receive adequate analgesia and sedation post-intubation in the EC (10). An American multi-centre study found that patients who were intubated using methods other than RSI and who have hypotensive episodes were more likely not to receive post-intubation sedation (11). Pre- and post-intubation hypotension may therefore be considerations as to why practitioners do not want to administer additional sedation or analgesia since the majority of these agents may exacerbate the hypotension (11). A study performed by C. Stein in 2017 investigating student paramedic RSI in Johannesburg is the only South African study commenting on post-intubation sedation practices. In this study it was found that only 72% and 63% of patients receive morphine and midazolam, respectively, post-intubation (6) post-intubation No other studies have been published that assesses post-intubation sedation and analgesia practices in the South African pre-hospital setting.

**Motivation**

Various disadvantages to poor or no administration of sedation and analgesia post-intubation have been described in the background section. Due to these potential detrimental effects, it is imperative to reiterate the consistent use of these agents post-intubation to mitigate the potential adverse effects. It can even be advisable to get a non-medically trained driver for the ambulance to allow for two practitioners to care for the patient during transport. There is very limited data in the literature regarding post-intubation sedation and analgesia practices in the emergency centre and even less in the pre-hospital setting. It must therefore, first be determined if this is a problem in the South African pre-hospital setting.

This study therefore aims to investigate if patients are routinely receiving sedation and analgesia post-intubation.
Aims and objectives

The aim of this study is to describe the pre-hospital post intubation sedation and analgesia practices in a South African private ambulance service.

Primary objectives

- To describe the proportion of patients who receive post-intubation sedation and/or analgesia post successful intubation.
- To determine the time to first sedation/analgesia intervention post successful intubation.
- To determine the number of sedation/analgesia administrations post successful intubation.

A sedation/analgesia intervention will be classified as administration of any amount of sedation or analgesia or an increase in an existing infusion of analgesia and/or sedation.

Secondary objectives

- To determine whether there is an association between analgesia and sedation administration and paralytic use
- To describe the association, if any, of clinical parameters (systolic blood pressure and heart rate) on the time/s to first and subsequent sedation/analgesia administration (early, late or omitted which will be defined post-hoc) as well as the mean number of sedation/analgesia interventions.

Research methodology

Study design

This will be a retrospective chart review study of patient report forms of ER24.

Study setting

ER24 is a national private ambulance service in South Africa that treat and transport various patients in a primary as well as a transfer setting. ER24 consists of ground and aeromedical transport.
ER24 employs advanced life support (ALS) practitioners of various qualifications who are permitted to intubate patients endotracheally using various means, including procedural sedation and rapid sequence intubation (RSI). A patient report form must be completed for every patient treated by an ER24 employee. On these patient report forms, it must be stated how many attempts at intubation was allegedly performed. Access to these patient report forms will be required in order to access the data needed to complete this study.

Sample

Inclusion criteria

- All patients successfully intubated by an ALS in the pre-hospital setting (during primary ground and aeromedical responses, as well as during interfacility transfers (patients who were intubated by the ALS prior to transfer),
- Successful intubation after first attempt (this is recorded on the patient report form),
- With either rapid sequence intubation medication or procedural sedation,
- Between 01 January 2017 and 31 December 2017,
- Patients of all ages

Exclusion criteria

- Patients in cardiac arrest,
- Endotracheal intubation not performed by ALS (patients intubated by a doctor),

Data collection and measurements

A patient report form is completed for every patient who is treated by an ER24 employee. These patient report forms are serially numbered and marked according to the ER24 branch that treated the patient. These patient report forms are electronically scanned by an external company and securely stored in an offsite facility to ensure that none of these reports are misplaced. The scanned electronic copies are available in a central ER24 billing system for record keeping and billing purposes. Various interventions performed on the patient are manually captured during the billing process to assist with the billing structure. These may include intravenous access, endotracheal intubation, cardioversion etc. The system can therefore easily be searched for endotracheal intubations.
An MMed Anaesthetic student at the University of Cape Town is conducting a research project titled “A retrospective, descriptive analysis of prehospital provider-performed emergency endotracheal intubation in a South African national private ambulance service”. During data collection of the MMed study, all intubations during the study period will have been captured. The relevant data that the MMed student is using in their study will be recorded from the patient report forms into an excel spreadsheet using the search station of the ER24 billing system. The excel data capture sheet of the MMed study will be used to identify the first pass success intubations and the original patient report forms of these intubations will then be obtained for data capture in the current study.

Only intubations that were successful after the first attempt will be included in this study. The reason for this is because time of intubation is not recorded on the patient report form. It will therefore not be possible to accurately determine the time of intubation if more than one attempt was made at intubation and subsequent doses of induction or additional sedation was administered for these attempts. If this was the case then it would be impossible to distinguish between post intubation sedation or additional sedation for follow up intubation attempts, unless it was written into the additional hand written notes of the ALS practitioner, which cannot be guaranteed.

Since the patient report forms that the MMed student used, will be reused for this study, the patient report forms have already been obtained and de-identified. Permission from ER24 has therefore already been obtained for the descriptive analysis by the MMed Anaesthetic student. Additional approval will be requested from ER24 for the current study.

The time of intubation will therefore be determined as the time where induction and neuromuscular blockade agents were administered during RSI or where the largest dose of procedural sedation medication was administered. The time of first sedation or analgesia administration will be determined as the next time any type of sedation or analgesia is administered. The difference between the two times will be calculated. The timeframes of these dosing regimens will be grouped after data capture. The number of sedation or analgesia administrations, adjustments to infusions and the dosing of these interventions will be recorded.

The timings recorded on patient report forms are often estimates and not very accurate. The methods described above is therefore to obtain the best possible time frame. The exact times however is not essential since the administration of the post intubation sedation will be grouped into ranges post hoc. These ranges will also be determined post hoc.
Data management

According to an article by Gilbert et al published in 1996, there are 8 strategies that can be applied to the methodology of a chart review study to improve the validity, reproducibility and the quality of the data extracted from the charts (17). These methodological strategies include training of the data extractor, case selection, clear definition of variables, data abstraction forms, meetings between data abstractors and monitoring of the abstractors for quality assurance, blinding of the abstractors and testing of the abstractor agreement. These strategies will be addressed as follows:

• Training: The primary researcher will be conducting the data abstraction, therefore no training will be needed. Of the total sample, 10% will be submitted to a secondary abstractor to perform data collection for quality assurance purposes. This abstractor will be a qualified Emergency Care Practitioner with experience in research and no direct involvement in the study. This abstractor will be familiar with the layout of the ER24 patient report forms, however, formal training regarding the study and data needed will be provided. The variables that need to be extracted is not open for interpretation since the data is quantitative in nature. If any discrepancies do arise on comparison of the primary and secondary abstractors’ data from the inter-rater reliability calculation, a third party will be obtained for resolution of these discrepancies as well as to investigate the reason behind this.

• Case selection: There will be strict inclusion and exclusion criteria. If these criteria decrease the sample size to such a degree that it is too small for meaningful interpretation, then the study period can be extended to intubations performed over 2 or 3 years.

• Definition of variables: the data will be quantitative so there will be no interpretation/definition of variables needed. The quantitative data will be recorded and statistically analyzed and the end product will be analysed in terms of significance. This will be done by the researcher, in conjunction with the supervisor to validate the interpretation. See appendix B

• Abstraction forms: A data abstraction form was created in an Excel spreadsheet and is contained in Appendix A.

• Meetings: Meetings will be held between the researcher/abstractor, the quality control abstractor and the supervisor to discuss problems with validity or discrepancies should they arise.
• Monitoring: There will be only one researcher/abstractor, therefore a quality controller assistant abstractor will extract a random sample and compare similarities to the primary researcher. Similarity is expected since the data is quantitative and not open to interpretation.
• Blinding: This will unfortunately be difficult to manage since there will only be one researcher. There is no hypothesis testing therefore blinding will not be necessary. Bias from non-blinding will be low since the data is quantitative.
• Testing of interpreter agreement: Agreement between inter-raters will be calculated with a kappa statistic assessment and included in the report of the study.

Additional criteria for chart review studies were identified by Worster et al (18). These criteria include medical record data base identification, missing data management plan, sampling method and institutional review board approval. The database was clearly defined in the study setting and data management section of this document. A purposive sampling method will be employed whereby all the first pass success intubations over a period of one year will be selected for data abstraction and analysis. The study will be submitted to the Faculty of Health Sciences Human Research Ethics Committee at the University of Cape Town for ethical approval.

The data will be recorded on a standard excel spreadsheet created by the primary researcher (Appendix A). Basic formulas will be written into the spreadsheet to calculate the time difference between induction and first sedation/analgesia administration post successful intubation as well as basic sum and percentage calculations. The data will be backed up on a secure server only accessible to the primary researcher with password protection.

**Missing data management**

Missing data or variables are often a limitation of retrospective chart reviews, especially when quantitative data is measured. Various strategies can be implemented to adjust for these missing variables. These include averaging of the data set, discarding the data set or substituting with a maximum likelihood strategy (19). Most of the patient report forms go through a quality control system by a designated person (usually the ALS practitioners) at each ER24 branch where they are written before they are submitted to the head office. The patient report forms are reviewed to ensure the time/s of medication administration and vital sign values are not omitted. As a result, it is the authors belief that missing data will be minimal. In the event that data is missing, it will be managed as follows:
• Missing times for medication administration before, during and after intubation – the PRF will be included for calculation of proportion of post intubation sedation administration, however, the PRF will not be included for analysis of time frame of post intubation sedation.

• Missing heart rate and blood pressure values – the heart rates and blood pressures that are present will be averaged for the missing set. If no blood pressures are present, then this one variable will be excluded from the sample and it will be assumed that this variable is missing at random (19).

Data analysis

Data analysis will be descriptive in nature. The data related to the primary objectives are largely categorical in nature and will be analysed and presented as proportions. This will include the number of cases where post-intubation sedation/analgesia of any form was administered and will be presented as a percentage. The percentages of early and late post-intubation sedation/analgesia will be presented and the mean number of sedation/analgesia administrations per case will be calculated.

Analysis of intubation via RSI with Suxamethonium or rocuronium, and procedural sedation intubations will be done separately. Mean time to sedation/analgesia administration post successful intubation will be calculated for each. These times will be compared using unpaired Student t-test or Mann-Whitney depending on the distribution of the results. Spearman's correlation or Pearson's test (depending on distribution) will be used to see whether time intervals for sedation/analgesia correlate with changes in vital signs.

Ethical considerations

This will be a retrospective chart review study. Thus, there will be no interventions that may require ethical approval. One ethical consideration may be patient confidentiality, since the patient medical records usually contain the personal details of each patient. However, the data sample will be obtained from the larger descriptive analysis done by an MMed Anaesthetic student, and these patient report forms have been de-identified, therefore no patient information will be visible. It will not be possible to obtain patient consent to utilise the clinical data, however no demographic or personal data will be captured; only clinical information will be extracted.
The researcher will keep all information confidential and stored in a secure, password protected location if the medical records are obtained in electronic form. The study will be submitted to the Faculty of Health Sciences Human Research Ethics Committee at the University of Cape Town for ethical approval.

**Limitations**

Selection bias is introduced since only the intubations that were successful on first attempt will be used for data collection and analysis. However, this is considered an acceptable bias for this particular study as there is no time stamp of successful intubation on the patient report forms and therefore no way to identify when intubation was successful after a second or third attempt. In the instances where additional sedation or a follow up induction dose was administered, there will be no way to differentiate whether this is a follow up induction dose for a subsequent intubation attempt or if it is post-intubation sedation. Therefore, only first pass success intubations will be selected and the induction dose with neuromuscular blockade or first and/or largest procedural sedation medication (morphine and midazolam) dosages will be used as the time of intubation. The succeeding sedation/analgesia administration time will be taken as the first post-intubation sedation administration. The exact time of intubation will therefore not be known, however the intubation time is not the objective. With a larger sample size, any small discrepancies should also be diluted.

The handwritten patient report form is often compiled after completion and handover of the emergency case. Recall bias can therefore be introduced as well as possible falsification of timings and vital signs not recorded during the incident (20). The only other way to conduct a study that assesses post-intubation sedation accurately is to have an external data capturer with every practitioner, recording the timing of medication and vital signs in real time. This is unfortunately not feasible and a retrospective chart review is the only way the determine current practice in the field.

**Data dissemination plan**

This study will be completed as part of the MPhil degree in Emergency Medicine. The final product will be available in the UCT library open access archive. The results of this study will be written up and submitted for publication in a peer reviewed journal. The results will also be made available to ER24 for their internal clinical governance purposes.
### Project timeline

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### Budget and resources

#### Budget

**July 2019 – February 2020**

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References


20 March 2020

HREC REF: 078/2020

Dr W Stassen  
Division of Emergency Medicine  
c/o Ms Vethiswe Mtambo  
F51, OMB

Dear Dr Stassen

PROJECT TITLE: A RETROSPECTIVE REVIEW OF POST-INTUBATION SEDATION AND ANALGESIA PRACTICES IN A SOUTH AFRICAN PRIVATE AMBULANCE SERVICE (SUB-STUDY - 706/2018) (MASTER'S DEGREE - JOALDA MARThINE DE KOCK)

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30 March 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Joalda de Kock will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN  
Chairperson, FHS Human Research Ethics Committee

Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
Appendix 6: ER24 Research Committee approval letter

Joaida Marthine de Kock
Division of Emergency Medicine
University of Cape Town

Dear Joaida,

RE: PROJECT 01/2020
PROJECT TITLE: A RETROSPECTIVE REVIEW OF POST-INTUBATION SEDATION AND ANALGESIA PRACTICES IN A SOUTH AFRICAN PRIVATE AMBULANCE SERVICE

The above research protocol has been reviewed by the ER24 Research Committee and I am pleased to inform you that your request has been approved.

The data required for you to execute this study had already been supplied to your supervisor, Dr Stassen, for a previous project. We hereby permit that you use this data set for your project.

Should your methodology change or any concerns arise during the data collection period, it is your responsibility to inform the ER24 Research Committee in due course. You are also required to forward the completed project to ER24.

I look forward to viewing the results of your study. I am positive that the science that you will generate will be of benefit to the profession.

Kind Regards

Signature Removed

Craig Wylie
Research Committee
ER24