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Practice of analgesia and sedation in adult mechanically ventilated patients in South African ICUs

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

Johannesburg, 2020

Declaration

I, Nicole Emaline Hendricks declare that this research report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

20 August 2020

Abstract

Background

Pain and agitation are experienced in the intensive care unit (ICU) during mechanical ventilation. There is a move toward analgesia and away from sedation to avoid the negative sequelae of sedation and to ensure a calm, comfortable patient. The ICU practice of analgesia and sedation have been described internationally, but not in South Africa.

Objectives

The aim of this study is to describe the practice of analgesia and sedation by doctors in adult mechanically ventilated patients in ICUs in South Africa.

Methods

This study used a descriptive, prospective, contextual study design. A convenience sampling method was used with distribution of a questionnaire at the Critical Care Society of Southern Africa congress in 2018.

Results

The Visual Analog Scale (VAS) and the Richmond Agitation-Sedation Scale (RASS) were the most used scales for analgesia and sedation assessment, respectively. Morphine was the drug most used for both analgesia and sedation. The benzodiazepine midazolam was the second most used sedative (31%). Non-pharmacological methods were used by 26.4% of respondents. Patients' clinical diagnosis was the main factor influencing the selection of analgesics and sedatives, which equated to 65.2% and 74.6%, respectively.

Conclusion

Analgesia and sedation assessment are performed by most doctors. Morphine is still commonly used, but the use of midazolam remains high despite evidence for its negative sequelae. These practices in ICU may be improved by training doctors in the assessment of patients, drug selection and the implementation of analgesia and sedation guidelines.

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Abbreviations

BPS	Behavioural Pain Scale
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CCSSA	Critical Care Congress of South Africa
CPOT	Critical Care Pain Observation Tool
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive Care Unit
NRS	Numeric Rating Scale
RASS	Richmond Agitation-Sedation Scale
VAS	Visual Analogue Scale

Statement

The Research Report consists of a literature review, draft article, study proposal and appendices. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the rest of the Research Report in order to comply with the author guidelines of the Southern African Journal of Critical Care, the journal to which it is intended to be submitted.

Section 1: Review of the literature

1.1 Introduction

Patients in the intensive care unit (ICU) who require mechanical ventilation, require an appropriate analgesia and sedation strategy to facilitate synchronous ventilation and to reduce pain, discomfort, anxiety and distress (1-4). Mechanically ventilated patients may not be able to describe their physical or emotional state and may experience pain, agitation and delirium (5-7). These patients require management of analgesics and sedatives with appropriate doses and monitoring of their therapeutic and adverse effects (3, 8, 9). The correct treatment of pain and agitation decreases negative outcomes and duration of mechanical ventilation in the ICU (4, 7, 10). The goal is to have a patient that is awake, calm and comfortable in order to facilitate mechanical ventilation with good patient outcomes (11).

This literature review will address the guidelines available as well as analgesia and sedation assessment and practice. Delirium is associated with the management of analgesia and sedation and will also be briefly discussed. In addition, a description of this practice from similar surveys in developed and developing countries will be discussed.

1.2 Brief overview of guidelines

The management of analgesia and sedation in ICU is an evolving practice that is reviewed and updated by experts in this field. There are national and international guidelines for this practice.

An analgesia and sedation guideline (12) was published in 1995 by the Society of Critical Care Medicine. In 2013, the Clinical practice guidelines for the management of pain, agitation and delirium in adult patients in the intensive care unit (4) was published. These guidelines contained recommendations for weaning from ventilation, the adverse effects of deep sedation, the use of assessment scales, new drugs, drug free methods and new approaches to analgesia and sedation. In 2018 the Clinical practice guidelines for the prevention and management of pain, agitation and sedation, delirium, immobility and sleep

disruption in adult patients in the ICU (7) expanded on the evidence in the 2013 clinical practice guideline.

The evidence and consensus-based guideline for the management of delirium, analgesia, and sedation in intensive care medicine, revision 2015 (11) was published by the European Society of Intensive Care Medicine for the early management of analgesia, sedation and delirium. Recommendations for assessment and treatment with goal directed therapy for pain and agitation were made in order to avoid the negative consequences of over sedation. Ideally, the patient should be pain free and not sedated.

The South African Society of Anaesthesiologists published two guidelines titled the South African Acute Pain Guidelines 2015 (13) and the South African Society of Anaesthesiologists Sedation Guidelines 2015 (14). These guidelines include sections for procedures on patients as well as briefly describing the management of analgesia and sedation in ICU. Both were developed by and co-authored by two different panels of experts.

Using information from these guidelines as well as additional evidence from experts in this field, the practice of analgesia, sedation and delirium will be discussed.

1.3 Analgesia practice

Pain is defined as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage” (15). Pain is experienced in ICU at rest, during procedures and mechanical ventilation (6, 16) but is not easily expressed by patients with altered consciousness (17). The appropriate management of pain in ICU reduces the need for sedation and may decrease patient morbidity, length of ventilation and ICU stay (18, 19). The analgesia practice regarding pain assessment and management will be discussed.

1.3.1 Pain Assessment

Pain assessment in ICU should be a consistent process to improve patient outcomes (18, 19), but it can be difficult. Observation of vital signs in the ICU

should prompt doctors to perform a bedside assessment for pain rather than used solely to determine the level of pain. According to the 2013 clinical practice guidelines, pain at rest should be considered a major clinical symptom (4).

A patient's ability to report pain is the gold standard of assessment. Practioners may use self-reported pain from patients with validated assessment scales. These include the Numeric Rating Scale (20, 21), the Verbal Rating Scale and the Visual Analogue Scale (VAS) (17, 22). The Numeric Rating Scale (23) is suggested as the most valid and easy to use (7). There are also validated pain assessment scales for patients who are unable to communicate their pain intensity (7, 18, 19). These bedside tests include the Behavioural Pain Scale (24) and the Critical Care Pain Observation Tool (25-27). These patients must have intact behavioural and motor function, which implies no sedation. The Behavioural Pain Scale has also been validated in sedated patients and patients with delirium. The Behavioural Pain Scale and Critical-care Pain Observation Tool may be used in combination (25) and may improve the assessment of analgesia.

1.3.2 Management of analgesia in the ICU

There are pharmacological and non-pharmacological methods to treat pain. Opioids are the recommended first choice for pharmacologic therapy (4, 7). Although the main effect of opioids is analgesia, they do provide some anxiolysis, but no amnesia (28). Opioids have a dose dependent effect on respiratory depression and in appropriate doses, they may help to suppress coughing and the perceived dyspnoea of patients on a ventilator (29). Opioids have adverse effects, such as a decrease in gastrointestinal motility. The introduction of newer opioid agonist-antagonists that target peripheral mu-2 receptors in the gastrointestinal tract may be an alternative solution to traditional opioid drugs (2). These newer opioids may be used to minimise adverse effects and tolerance while still providing analgesia.

The addition of non-opioid multimodal analgesia may be used to decrease opioid use and opioid related adverse effects. These non-opioid analgesics include non-steroidal anti-inflammatory drugs, intravenous acetaminophen, ketamine and neuromodulating drugs (gabapentin and carbamazepine), which are usually

reserved for neuropathic pain (4). Ketamine has been evaluated for use in ICU (30) and was found to be safe, effective and associated with a decrease in opioid use when used for analgesia and sedation. In addition to non-opioid analgesics, the alpha 2 agonists, clonidine and dexmedetomidine may be used as adjuvants to analgesia (31, 32). Although initially introduced as a novel short term sedative due to its sedation and anxiolysis, dexmedetomidine also provides analgesia with less respiratory depression than other sedatives (31) and may be used to reduce the requirement for opioids and as part of opioid-sparing techniques (8).

Non-pharmacological interventions are defined as “therapies that do not involve taking medicines or any other active substances” (17). These techniques may enhance analgesia as part of a multimodal approach. Non-pharmacological methods include cyber therapy (virtual reality), hypnosis, cold therapy, massage and music therapy (33). There is only a limited role for these techniques (7). There is still a paucity of evidence regarding non-pharmacologic methods.

A focus on adequate analgesia before sedation may result in reduced mechanical ventilation, a reduced ICU stay (34) and reduced cognitive complications (35). The appropriate use of analgesia when it also provides some sedation is known as “analgosedation” (36).

1.4 Sedation practice

Agitation occurs when there is excessive motor activity associated with disorganised thought and actions (37). Agitation as well as anxiety are experienced by patients in ICU (4, 7, 38). They may be symptoms of underlying causes, which include pain, delirium, hypoxia, physiological changes, drug withdrawal syndromes, excessive stimulation and sleep disturbances (38, 39). Sleep disturbances during mechanical ventilation are multifactorial. Higher doses of sedative drugs may be a contributing cause (40). Sedation was previously used to achieve a state of calm and anxiolysis (3, 41) but there has been shift away from the use of sedation unless it is specifically indicated (11, 35). Patients have improved outcomes if they are awake, oriented and mobilising in the ICU (11). Sedatives cause increased patient morbidity, duration of ventilation and length of ICU stay, especially when deep sedation is used for prolonged periods. The

sedation practice regarding assessment and management will be briefly discussed and the concept of delirium will be introduced.

1.4.1 Sedation assessment

The goal in ICU should be to ensure a comfortable and awake patient that is synchronous with mechanical ventilation. If any level of sedation is indicated, sedation assessment scales must be used (11) to prevent prolonged mechanical ventilation and over sedation (4, 42) which results in negative outcomes (43, 44).

Sedation assessment scales that are validated for use in the ICU are used to distinguish between calm and agitated patients. The most common sedation scales used are the Richmond Agitation-Sedation Scale (RASS) (45), the Riker Sedation Agitation scale (46), the Ramsay Sedation Scale (47) and the Motor Activity Assessment Scale (48). The RASS and the Riker sedation agitation scale are recommended as the most valid and reliable tools for the quality and depth of sedation (4). Both scales use clearly defined criteria for levels of sedation and agitation. The RASS is easy and quick to perform (6). The South African Society of Anaesthesiology consensus guideline for sedation (14) also suggests tools for assessment of sedation which include the Wilson sedation scale (49) and the University of Michigan sedation scale (50).

If sedation is used, the goal should be for light sedation that is regularly assessed. If there is a need for increasing depth of sedation, there should be a defined level of sedation and a defined time for assessment and review (11). Daily interruption of sedatives may be used when assessing patients with deep sedation but it is not superior to the use of a protocol (51).

1.4.2 Management of sedation in the ICU

There are pharmacological and non-pharmacological methods used to sedate patients (2, 3, 41, 52). The use of sedatives may be the cause of delirium and cognitive impairment, however, there are specific indications for the use of sedation which include airway protection and neurological protection.

Sedative hypnotics, which include benzodiazepines, and intravenous induction agents, which include propofol, may be used to sedate patients (53).

Benzodiazepines bind to specialised receptors in the brain to provide anxiolysis, amnesia, sedation and anticonvulsant activity (28) but they do not provide analgesia. The adverse effects of benzodiazepines include tolerance and delayed emergence (54). Although midazolam is still used, there is increasing use of non-benzodiazepine drugs such as propofol and dexmedetomidine (55-57). A systematic review (58) concluded that non-benzodiazepine sedation results in a shorter length of ICU stay and a shorter duration of mechanical ventilation. In studies comparing midazolam, propofol and dexmedetomidine in ICU, dexmedetomidine resulted in a shorter duration of mechanical ventilation (59) and less delirium (60).

Propofol provides anxiolysis, amnesia, sedation, hypnosis, antiemetic and anticonvulsant activity but does not provide analgesia (61, 62). It has a more favourable pharmacokinetic profile when compared to benzodiazepines, however, it may alter blood pressure and heart rate in a dose dependent manner. An important adverse effect of using propofol is the propofol infusion syndrome (63, 64) due to propofol toxicity. Critically ill patients may be more susceptible to develop this toxicity which usually presents when high dose (> 4mg/kg/hr) propofol infusions are used for more than 48 hours (65). This causes impaired mitochondrial function with disruption of the electron transport chain, adrenoreceptors and cardiac calcium channels. It results in a severe metabolic derangement with metabolic acidosis, rhabdomyolysis, hyperkalaemia, acute kidney injury, raised liver enzymes and cardiac dysfunction. It is managed with supportive management but has a high mortality rate (63).

Dexmedetomidine binds selectively to alpha 2 receptors in the central nervous system and provides sedation, analgesia and sympatholysis (66). Dexmedetomidine is synergistic with opioids (60), may be used safely and predictably for longer periods in ICU (67) and reduces the duration of mechanical ventilation (68). Dexmedetomidine is also associated with a dose dependent increase in bradycardia and hypotension (69).

Sedation causes changes in the normal circadian rhythm and sleep patterns which affects patients adversely (40). Benzodiazepine drugs adversely affect normal sleep patterns. Propofol also affects normal sleep and at high doses can induce

burst suppression on the electroencephalogram (40). Dexmedetomidine at night may assist in improved sleep patterns during mechanical ventilation. There is, however, evidence for use of drugs other than sedative drugs such as melatonin for the stimulation of a normal circadian rhythm and sleep during mechanical ventilation in the ICU (70).

Non-pharmacological methods may be used to promote calm and comfort. These include cognitive stimulation, improved sleep hygiene, sensory aids and a reduction of bright light and noise (7). Restraints to restrict patients' movement in ICU may be used (71) and includes physical restraints, such as bed sides and wrist belts, as well as chemical restraints (72, 73). There are important physical, psychological and ethical considerations for the use of restraint but it is often justified to avoid patient harm (71). It can also be considered as a violation of the patients' rights unless its use maintains the patients' dignity (74) and it is used with informed consent (75). The prevalence of physical restraints among ICUs is only described in the PADIS guideline but there are no recommendations for or against its use (7).

Sedative agents and increasing depth of sedation are risk factors for the development of delirium. "Rapidly reversible, sedation-related delirium" may improve after sedation is stopped, but it is still associated with negative outcomes (76). The assessment, prevention and treatment of delirium will be discussed below as its prevalence is one of the factors that has altered the management of sedation in ICU.

1.4.3 Delirium

Delirium is a syndrome defined by the Diagnostic and Statistical Manual of Mental Disorders (77) that includes a fluctuating mental status ranging from an altered level of consciousness to inattention, disorganised thinking and confusion (78). Together with a change in cognition, this constellation of signs are important features of delirium (79). Delirium may be hypoactive or hyperactive and results in a worse outcome following ICU admission (1, 79). Patients are on the spectrum of delirium from psychomotor retardation to agitation associated with 'combative'

behaviour. Hypoactive delirium is more common and associated with a poorer prognosis.

Delirium may still be under recognised and inadequately assessed in patients who are sedated. There are two assessment scales validated for use in the ICU that include the Confusion Assessment Method for ICU (80) and the Intensive Care Delirium Screening Checklist (81). These may be used to assess patients in ICU who are increasingly awake and not sedated.

There are modifiable and non-modifiable risk factors for delirium which include pre-existing patient illness, sedation, immobility, and sleep disruption (82). Benzodiazepines may be an independent risk factor for delirium in the ICU (83) and in a randomised control trial comparing midazolam or propofol to dexmedetomidine in ventilated patients, the patients who received dexmedetomidine had more delirium free days (84).

There are also pharmacological and non-pharmacological methods to prevent and treat delirium. Atypical antipsychotics may be considered for prevention and treatment and include haloperidol, risperidone, quetiapine, olanzapine and ziprasidone (85). Is uncertain if different agents should be used for the hyperactive versus hypoactive form of delirium and there is no strong recommendation for one drug over the other (86). There is only a small study in which quetiapine was used and resulted in a shorter treatment period with earlier discharge (87). Non-pharmacological methods are similar to those used for sedation and include an appropriate ICU environment, early mobilisation and sleep (76).

There is a balance between prevention, assessment and treatment of pain, agitation and delirium in ventilated patients in the ICU. A description of the practice of analgesia and sedation is important to determine the need for further education, support and training.

1.5 Review of analgesia and sedation practice

The practice of analgesia and sedation has been described in other countries and there may be differences between developed and developing countries (88) and between ICUs (1, 8). While procedural sedation practices have been described

and published in South Africa, there is a paucity of data describing analgesia and sedation practices in mechanically ventilated patients in ICU in the African and South African context. The evolution of the practice of analgesia and sedation is evident in the following review of surveys in other countries.

1.5.1 Review of analgesic and sedation practice

A survey of physicians endorsed by the European Society of Intensive Care Medicine concluded that implementation of guidelines does vary (89). Eighty-three percent did assess pain and 61% sedation. Delirium was assessed by 40% routinely.

A study describing the use of analgesia and sedation in mechanically ventilated patients internationally by region included the regions; Europe, The United States of America, Canada, Australia, New Zealand, Africa, Asia and Latin America (90). The use of opioids from 2010 to 2016 increased similarly across all regions. The highest use of benzodiazepines was in 2010 in Africa and Latin America. There was little change in the overall use of benzodiazepines in Africa by 2016. There was an increased use of dexmedetomidine in 2016 with the highest use reported in Asia.

In a survey of Spanish ICUs (91) pain assessment was performed using the VAS by 52.8% and sedation using the RASS by 84.9%. There were 12.2% who used fentanyl for analgesia and 16.7% who used midazolam for sedation. Very few ICUs reported the use of non-pharmacological techniques.

A survey in the People’s Republic of China (92) showed that analgesia assessment was performed by 75.8% of doctors of which most, 46.4%, used the VAS. Sedation assessment was performed by 68.9%. There were 56.7% who used the RASS. Delirium was assessed by 66.7%. There were 65.5% who used fentanyl for analgesia and 85.5% who used midazolam for sedation.

A survey in the United Kingdom (93) showed that 93.9% assessed sedation and 64.7% used the RASS to assess sedation. Delirium was assessed by 69.6%. Sedation was achieved using propofol by 98.1%, however 32% still used midazolam.

An online survey was conducted in India by the Indian Society of Critical Care Medicine and the Indian Society of Anaesthesiologists (94). Analgesia assessment was performed by 48.1% using the VAS. Sedation assessment was performed using the Ramsay scale (56.1%). There were 47.0% who used fentanyl for analgesia and 95% sedation was achieved using midazolam. There were 34.4% respondents who assessed for delirium.

A survey by the French Intensive Care Society (95) showed a shift away from deep sedation. Analgesia assessments were performed mostly by nurses using the behavioural pain scale, while sedation was assessed using the Ramsay sedation scale or the RASS. Sufentanil was the opioid of choice and sedation was achieved using midazolam and propofol. Non-pharmacological analgesic practice was not reported.

A survey in Brazil (96) showed that sedation assessment was performed by most doctors using the Ramsay sedation scale. Delirium was assessed by most doctors using the confusion assessment method for ICU. Fentanyl was used by 91% of respondents. Sedation was achieved using midazolam and propofol. Most participants also agreed that patients were usually over sedated.

A survey in Malaysia (97) showed that sedation assessment was performed by only 35% of doctors, of which the majority used the Ramsay sedation scale and their own clinical experience. Most used morphine for analgesia and sedation was achieved by the majority using midazolam.

A survey in Canada (98) showed that sedation assessment was performed by 49% of doctors using the Ramsay scale. Delirium was only assessed by 3.7% of doctors. The most commonly used drug was morphine for analgesia and midazolam for sedation.

1.6 Summary

This literature review discusses the essential components of the practice of analgesia and sedation in mechanically ventilated patients in ICU. In order to ensure comfort, calm, improved ventilator synchrony and prevent complications, a

balance of prevention, assessment, appropriate drug selection and non-pharmacological methods may be used. The evidence is in constant evolution.

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Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The title of the manuscript should concisely describe the study but should not include the outcome. The introduction should be concise – no more than three paragraphs – on the background to the research question and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are to fill a gap in the literature, a logical extension of previous work, or to answer an important question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. At the end of the introduction clearly state the aim or objective of the study. The primary and secondary outcomes should be specified.

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- May include up to 6 illustrations or tables.

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o Objectives: what the study intends to find out

o Methods: must include study design, number of participants, description of the research tools/instruments, any specific analyses that were done on the data.

o Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

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o Do not include any references in the abstracts.

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These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Narrative review articles should always be discussed with the Editor prior to submission. (Structured reviews or meta-analyses' need not be).

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Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important

- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.

- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations and provide advice specific to southern Africa.

- Personal details: Please supply your qualifications, position and affiliations address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

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- May include only one illustration or table
- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner’s death and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
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- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.

- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.

- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.

- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.

- Ensure each table has a concise title and column headings and include units where necessary.

- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting.

- Authors must verify references from original sources.

- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others [3,4-6]

- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).

- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.

- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.

- Volume and issue numbers should be given.

- First and last page, in full, should be given e.g.: 1215-1217 not 1215-17.

- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:

  - On the CrossRef homepage, paste the article title into the ‘Metadata search’ box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
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Some examples:

- Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. DOI:10.1000/hgjr.182
- Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

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- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

- Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

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o Manuscript

o Ethics Approval form (for research articles)

o Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.

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2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.

4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.

5. The CE will finalise the article and then it will be typeset.

6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.

7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.

8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

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Errata and retractions

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4. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (Jpeg). These must be submitted as 'supplementary files' (not in the manuscript).

5. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.

6. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).

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8. The research was approved by a Research Ethics Committee (if applicable)

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Section 3: Draft article

Practice of analgesia and sedation in adult mechanically ventilated patients in South African ICUs

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Abstract

Background

Pain and agitation are experienced in the intensive care unit (ICU) during mechanical ventilation. There is a move toward analgesia and away from sedation to avoid the negative sequelae of sedation and to ensure a calm, comfortable patient. The ICU practice of analgesia and sedation have been described internationally, but not in South Africa.

Objectives

The aim of this study is to describe the practice of analgesia and sedation by doctors in adult mechanically ventilated patients in ICUs in South Africa.

Methods

This study used a descriptive, prospective, contextual study design. A convenience sampling method was used with distribution of a questionnaire at the Critical Care Society of Southern Africa congress in 2018.

Results

The Visual Analog Scale (VAS) and the Richmond Agitation-Sedation Scale (RASS) were the most used scales for analgesia and sedation assessment, respectively. Morphine was the drug most used for both analgesia and sedation. The benzodiazepine midazolam was the second most used sedative (31%). Non-pharmacological methods were used by 26.4% of respondents. Patients' clinical diagnosis was the main factor influencing the selection of analgesics and sedatives, which equated to 65.2% and 74.6%, respectively.

Conclusion

Analgesia and sedation assessment are performed by most doctors. Morphine is still commonly used, but the use of midazolam remains high despite evidence for its negative sequelae. These practices in ICU may be improved by training doctors in the assessment of patients, drug selection and the implementation of analgesia and sedation guidelines.

Introduction

Pain and agitation in the intensive care unit (ICU) are experienced at rest, during procedures and during mechanical ventilation (1, 2). The use of guidelines, validated assessment tools, and an understanding of the pharmacologic and non-pharmacologic options available form part of this practice (3, 4). Guidelines have been published and include those from the Society of Critical Care Medicine (5, 6), the European Society of Intensive Care Medicine (7) and the South African Society of Anaesthesiologists (8, 9). The goal is to ensure a calm, comfortable and awake patient.

Pain is a serious concern in the critically ill patient (10) and is often the most common memory during the patient's ICU stay (11). The incorrect assessment and management of pain can be deleterious (12). Validated pain assessment scales include the Visual Analogue Scale (13), Numeric Rating Scale (14), Behavioural Pain Scale (15) and the Critical-care Pain Observation Tool (16). Analgesia includes the use of opioid or non-opioid analgesics and non-pharmacological methods. Analgesia that provides "analgosedation" (17) and an awake, oriented patient is important to decrease the duration of mechanical ventilation and ICU stay (7, 18).

Agitation and anxiety are nonetheless experienced in ICU (5-7) and may be symptoms of underlying causes, which include pain and delirium (19). Sedation is only used for specific indications where a defined depth of sedation and time for review of sedation must be prescribed. This may include the use of assessment scales such as the Richmond Agitation-Sedation Scale (RASS) (20), the Riker Sedation Agitation scale (21), the Ramsay scale (22) and the Motor Activity Assessment Scale (23). Sedation includes the use of benzodiazepines and non-benzodiazepine sedatives as well as non-pharmacological methods. The use of sedatives is not recommended routinely in these patients unless a specific indication is present (7). Importantly, the use of sedatives may be a cause for agitation in the form of delirium. Delirium affects 60 ─ 80% of mechanically ventilated patients (24). Patients may be on a spectrum of psychomotor retardation to agitation, referred to as hypoactive or hyperactive delirium, respectively. The presence of delirium results in worse outcomes (19, 24).

Delirium may be assessed using the Confusion Assessment Method for the ICU (25) and the Intensive Care Delirium Screening Checklist (26). In the patient who is not sedated, these are the preferred assessment scales for calm or agitation (7). Prevention and treatment of delirium may be considered using pharmacological and non-pharmacological methods (27). Antipsychotics, both typical and atypical, may be used.

The practice of analgesia and sedation have been described internationally (28-33) but not in South Africa. The aim of this study was to describe the practice of analgesia and sedation by doctors in adult mechanically ventilated patients in ICUs in South Africa.

Methods

Approval to conduct the study was obtained from the Human Research Ethics Committee (Medical) and other relevant authorities. This study used a descriptive, prospective, contextual study design.

The study population consisted of public and private sector doctors who attended the annual 2018 Critical Care Society of Southern Africa congress. The sample size was realised by the response rate, and a minimum of 60% was considered adequate. A convenience sampling method was used.

A previously unpublished questionnaire was identified as appropriate for use and was adapted following permission from the authors. The draft questionnaire was reviewed by three senior intensivists to ensure content and face validity and their recommendations were incorporated. The final questionnaire consisted of; respondent demographics, pharmacological analgesia and sedation practice, non-pharmacological analgesia and sedation practice and factors or challenges influencing analgesia and sedation.

The study was advertised in between presentations at the congress. Questionnaires were distributed by one author (NH) during the congress. Data were collected on three days of the congress. Participants were requested to return the completed questionnaire to a sealed collection box placed at the

CCSSA information desk. Blank and incomplete questionnaires with more than 50% incomplete were excluded from the study.

A Microsoft ® Office Excel spreadsheet was used to capture the data. Data were analysed with the assistance of a biostatistician using STATA version 15 (StataCorp, USA). Categorical variables were described using numbers and percentages. Associations between categorical variables and the public and private sectors were made using the Fisher's exact test. A p-value of < 0.05 was considered statistically significant. In the results section where the number of respondents does not reflect the total, respondents were able to choose more than one option per question.

Results

A total of 320 doctors attended the CCSSA congress. There were 209 questionnaires received of which 16 were excluded. The response rate was 193 (60.3%) The characteristics of the respondents are shown in Table 1.

Table 1 – Characteristics of respondents

Characteristics	n (%)
Sector	
Public	92 (47,7)
Private	56 (29,0)
Both	44 (22,8)
Not answered	1 (0,5)
Position	
Part-time and full-time intensivists	80 (41,5)
Interest in critical care	112 (58,0)
Not answered	1 (0,5)
Speciality	
Anaesthesiology	87 (45.1)
Internal medicine	41 (21,2)
General surgery	25 (13,0)
Paediatrics	9 (4,7)
Other	31 (16.1)
Subspeciality	
Critical care	66 (34,2)
Pulmonology	25 (13,0)
Other	3 (1.6)
Not applicable	95 (49,2)
Not answered	4 (2,1)

Respondents reported that 61.5% (range 5% ─ 100%) of their ICU patients required mechanical ventilation. Guidelines for analgesia and sedation were used by 162 (83.9%) respondents. National guidelines (8, 9) are used by 70 (36.3%) respondents. There were 58 (30.1%) respondents who used a combination of national and international guidelines and 34 (17.6%) who used the Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit (5) or the Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (6). The rest were not used by, not known by or not answered by 12 (6.2%), 17 (8.8%) and 2 (1.0%) respondents respectively. A protocol for analgesia was used by 84 (43.5%) respondents and a protocol for sedation was used by 81 (42.0%) respondents. Two (1.0%) respondents did not answer the question.

The use of analgesia and sedation assessment scales is shown in Figure 1. There were 41 (21.2%) respondents who did not know or use a pain scale and 1 (0.5%) who did not answer the question. There were 16 (8.3%) respondents who did not know or use a sedation scale. The assessment of delirium was performed routinely, sometimes and not at all by 48 (24.9%), 81 (42.0%) and 61 (31.6%) respondents, respectively. There were 3 (1.6%) participants who did not answer this question.

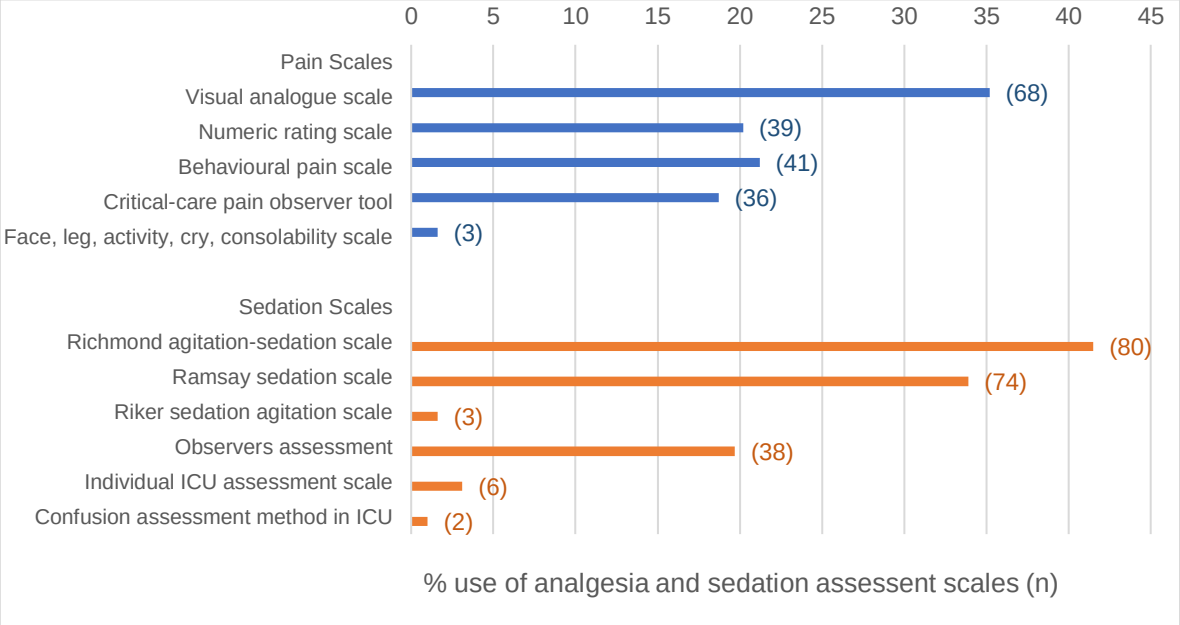


Figure 1 – Analgesia and sedation assessment scales used

Analgesia, sedation and delirium practices in the public and private sector are shown in Table 2. In addition, a comparison between the use of protocols for analgesia (p=0.0405) and sedation (p = 0.7318) as well as the assessment of delirium (p = 0.2254) was made. There was a statistically significant difference between the public and private sector use of analgesia protocols, with there being significantly less use in the private sector.

Table 2 – Analgesia, sedation and delirium practices in public and private ICUs

	Public n (%)	Private n (%)	Both n (%)
Number of respondents	92 (47,7)	56 (29,0)	44 (22,8)
Analgesia protocols used	46 (50,0)	18 (32,1)	20 (45,5)
Sedation protocols used	45 (48,9)	16 (28,6)	20 (45,5)
Analgesia assessment	BPS 23 (25,0)	VAS 29 (51,8)	VAS 19 (43,2)
	VAS 20 (21,8)	NRS 12 (21,4)	NRS 13 (29,6)
Sedation assessment	RASS 40 (43,5)	Ramsay 25 (44,6)	RASS 19 (43,2)
	Ramsay 33 (35,9)	RASS 21 (37,5)	Ramsay 16 (36,4)
Routine delirium assessment	17 (18,5)	15 (26,8)	16 (36,4)
Analgesic most used	Morphine 85 (92,4)	Morphine 31 (55,4)	Morphine 38 (86,4)
	Fentanyl 36 (39,1)	Dexmedetomidine 28 (50,0)	Dexmedetomidine 13 (29,6)
Sedative most used	Morphine 47 (51,1)	Dexmedetomidine 28 (50,0)	Morphine 19 (43,2)
	Midazolam 32 (34,8)	Morphine 14 (25,0)	Propofol 18 (41,0)
Factor affecting selection of analgesics	Availability 71 (77,1)	Diagnosis 42 (75,0)	Diagnosis/availability 27 (61,4)
Factor affecting selection of sedatives	Duration of ventilation 73 (79,4)	Diagnosis 44 (78,6)	Diagnosis 35 (79,6)
Challenge to analgesia practice	Limited choice of analgesics 29 (31,5)	Compliance with prescription by team 12 (21,4)	No uniform analgesia protocol 8 (18,2)
Challenge to sedation practice	Limited choice of sedatives 40 (43,5)	Compliance with prescription by team 15 (26,8)	No uniform sedation protocol 11 (25,0)

The frequency and timing of analgesia and sedation scales is shown in Table 3.

Table 3 – Frequency and timing of analgesia and sedation

Analgesia assessment n (%)						
	Not at all	**Not very often**	**Some of the time**	**Most of the time**	**All the time**	**Not answered**
First admission	38 (19,7)	21 (10,9)	24 (12,4)	54 (28,0)	54 (28,0)	2 (1,0)
Day shift	31 (16,1)	20 (10,4)	37 (19,2)	76 (39,4)	24 (12,4)	5 (2,6)
Night shift	35 (18,1)	35 (18,1)	46 (23,8)	57 (29,5)	16 (8,3)	4 (2,1)
Sedation assessment n (%)						
	Not at all	**Not very often**	**Some of the time**	**Most of the time**	**All the time**	**Not answered**
First admission	23 (11,9)	24 (12,4)	38 (19,7)	47 (24,4)	60 (31,1)	1 (0,5)
Day shift	22 (11,4)	25 (13,0)	41 (21,2)	61 (31,6)	41 (21,2)	3 (1,6)
Night shift	21 (10,9)	31 (16,1)	51 (26,4)	56 (29,0)	32 (16,6)	2 (1,0)

Respondents reported that sedation was received by 58.3% (range 0% ─ 100%) of patients. A mild, moderate and heavy depth of sedation was maintained by 66 (34.2%), 89 (46.1%) and 5 (2.6%) respondents, respectively. There was 1 respondent who selected both the mild and no sedation options. There were 31 (16.1%) respondents who did not use sedation and 3 (1.6%) respondents who did not answer the question.

Interruption of sedation was practiced routinely, sometimes and not at all by 112 (58.0%), 51 (26.4%) and 28 (14.5%) respondents, respectively. There were 2 (1.0%) respondents who did not answer the question.

Multimodal analgesia was prescribed to 58.0% (range 0% ─ 100%) of patients. There were 18 (9.3%) respondents who did not answer this question. The analgesic and sedative drug practices of respondents are shown in Table 4. The other analgesics that were most used were paracetamol by 10 (5.2%), ketamine by 2 (1.0%) and tramadol (3.1%) respondents. The other analgesics that were most preferred were paracetamol by 9 (4.7%) respondents, ketamine by 6 (3.1%) and oxycodone by 1 (0.5%). The other sedatives that were most used were ketamine by 8 (4.1%), tricyclic antidepressants by 1 (0.5%), diazepam by 1 (0.5%) and buprenorphine (0.5%). The other sedatives that were most preferred were ketamine by 10 (5.2%), tricyclic antidepressants by 1 (0.5%), clonidine by 1 (0.5%) and haloperidol by 1 (0.5%).

Table 4 – Analgesic and sedative drug practices

Analgesics n (%)				
	Most used	**Most preferred**	**Not used**	
Morphine	154 (79,8)	80 (41,5)	0 (0,0)	
Fentanyl	55 (28,5)	17 (8,8)	45 (23,3)	
Sufentanil	0 (0,0)	13 (6,7)	124 (64,2)	
Alfentanil	0 (0,0)	2 (1,0)	155 (80,3)	
Remifentanil	18 (9,3)	32 (16,6)	83 (43,0)	
Dexmedetomidine	44 (22,8)	96 (49,7)	50 (25,9)	
Other	18 (9,3)	16 (8,3)		
Sedatives n (%)				
	Most used	**Most preferred**	**Not used**	**Considered for weaning**
Propofol	53 (27,5)	34 (17,6)	30 (15,5)	30 (15,5)
Dexmedetomidine	57 (29,5)	125 (64,8)	62 (32,1)	115 (59,6)
Remifentanil	10 (5,2)	27 (14,0)	93 (48,2)	15 (7,8)
Midazolam	60 (31,1)	31 (16,1)	35 (18,1)	13 (6,7)
Morphine	80 (41,5)	36 (18,7)	30 (15,5)	33 (17,1)
Other	11 (5,7)	13 (6,7)		

Non-pharmacological methods were used by 51 (26.4%) respondents who listed physiotherapy, 4 (2.1%), distraction, 4 (2.1%), verbal reassurance, 2 (1.0%), cognitive support, 1 (0.5%), a change of patient position, 1 (0.5%), early removal of invasive tubing, 1 (0.5%) and a reduction in noise and bright light in ICU by 1 (0.5%) respondent. There were 183 (94.8%) respondents who used physical restraints. Consent was obtained by 70 (38.3%), a protocol was used by 98 (53.6%) and 1 (0.5%) respondent did not answer the question.

The factors that influence the selection of analgesics and sedatives are shown in Figure 2. There were 2 (1.0%) respondents who did not answer.

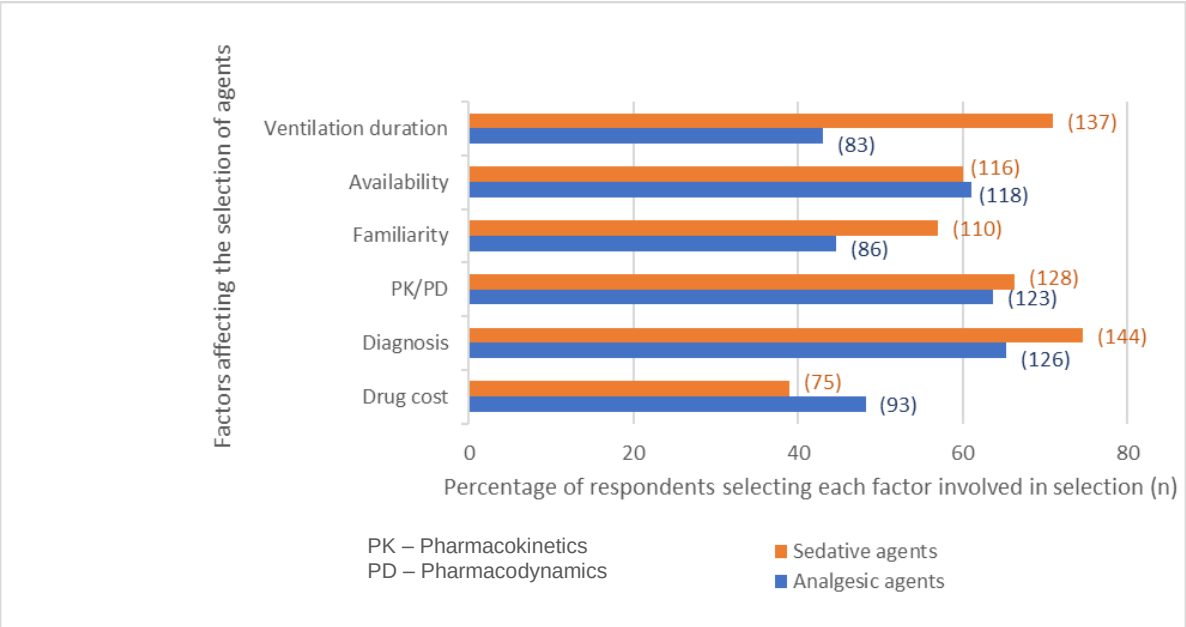


Figure 2 – Factors affecting the selection of analgesics and sedatives

The challenges to analgesia and sedation practice are shown in Table 5.

Table 5 – Challenges to analgesia and sedation practice

Analgesia practice challenge	**n (%)**		
	Challenge	**No challenge**	**Not answered**
Uniform written guidance	144 (74,6)	48 (24,9)	1 (0,5)
Compliance with prescription from your team	158 (81,9)	34 (17,6)	1 (0,5)
Weaning off ventilation	166 (86,0)	26 (13,5)	1 (0,5)
Ensuring compliance of protocol	161 (83,4)	31 (16,1)	1 (0,5)
Limited choice of agents	153 (79,3)	40 (20,73)	0 (0,0)
Need to reduce patient length of stay	165 (85,5)	27 (14,0)	1 (0,5)
Sedation practice challenge	**n (%)**		
	Challenge	**No challenge**	**Not answered**
Uniform written guidance	131 (67,9)	57 (29,5)	5 (2,6)
Compliance with prescription from your team	154 (79,8)	34 (17,7)	5 (2,6)
Weaning off ventilation	168 (87,0)	21 (10,9)	4 (2,1)
Ensuring compliance of protocol	161 (83,4)	26 (13,5)	6 (3,1)
Limited choice of agents	162 (83,9)	28 (14,5)	3 (1,6)
Need to reduce patient length of stay	169 (87,6)	17 (8,8)	7 (3,6)
High percentage experiencing delirium	179 (92,7)	7 (3,6)	7 (3,6)

There were 128 (66.3%) respondents who reported a need for a change of the practice of analgesia and sedation and 67 (34.7%) respondents who subsequently did not answer the follow-up question about the reasons for change. The reasons for change were reported by respondents as; new guidelines, 65 (33.7%), availability of drugs, 46 (23.8), expert opinion, 45 (23.3%), current publications, 24 (12.4%) and cost, 22 (11.4%). Other reasons listed by respondents included the off-label use of dexmedetomidine, 2 (1.0%), uncertainty, 2 (1.0%), disagreements in a closed ICU, 1 (0.5%) and nursing compliance, 1 (0.5%).

The important areas of support and training reported by respondents to improve the practice of analgesia and sedation are shown in Table 6.

Table 6 – Areas of support and training to improve the practice of analgesia and sedation

Support	n (%)		
	Needed	Not needed	Not answered
Greater choice of analgesic agents	160 (82,9)	32 (16,6)	1 (0,5)
Greater choice of sedative agents	163 (84,5)	28 (14,5)	2 (1,0)
Written protocols in the unit	145 (75,1)	43 (22,3)	4 (2,1)
Establishment of delirium assessment criteria	165 (85,5)	25 (13,0)	3 (1,6)
Earlier mobilisation and exercise	166 (86,0)	23 (11,9)	4 (2,1)
Training	**n (%)**		
	Needed	**Not needed**	**Not answered**
Assessment of pain	152 (78,8)	40 (20,7)	1 (1,0)
Assessment of agitation	160 (82,9)	30 (15,5)	3 (1,6)
Reduced complication from sedation	159 (82,4)	27 (14,0)	6 (3,1)
Ensuring compliance with protocols	165 (85,5)	25 (13,0)	2 (1,0)
Reducing ventilator days after infusions	169 (87,6)	20 (10,4)	4 (2,1)

Discussion

There has been a shift of focus prioritising the management of analgesia in the ICU and limiting the addition of sedatives to avoid the negative sequalae of sedation. There are specific clinical indications for the use of sedatives in the ICU (7). The benefits of reduced or no sedation are a reduction in delirium, duration of mechanical ventilation and length of ICU stay (7, 18, 19).

Mechanically ventilated patients frequently experience pain and agitation (2). Respondents in this study reported a varied range (5% ─ 100%) of patients requiring mechanical ventilation in ICU. Their exposure to the practice of analgesia and sedation may be reflected by this range or the range may reflect the clinical status of patients accepted to their ICUs.

The pain assessments that are commonly used are the Visual Analogue Scale, the Numeric Rating Scale, the Behavioural Pain Scale and the Critical-care Pain Observation Tool. There were 55.4% of respondents in this study who used the Visual Analogue Scale and the Numeric Rating Scale for assessment, which may reflect fewer sedated patients and more patients with the ability to self-report pain. These self-reported assessment scales were also used in studies in Turkey, 82.7% (31), Spain, 80.4% (30), The People's Republic of China, 61.3% (29) and

India, 63.8% (32). The most important factors influencing the choice of analgesic used was the patient's clinical diagnosis (65.2%) and the drug pharmacology (63.7%). Morphine (79.8%) was the most used drug in this study. Morphine is an analgesic that may be used for analgesia and sedation as it provides analgesia as well as a sedative effect without the addition of a sedative drug. In an international survey of 47 countries affiliated to the European Society of Intensive Care Medicine, morphine (78%) was the most used analgesic (28). This study compares similarly to the use of morphine internationally. Fentanyl, 28.5%, was the second most used drug in this study but it was the most used analgesic in studies in Spain, 12.2% (30), The People's Republic of China, 65.5% (29) and India, 47.0% (32). The drug most used in studies in other countries was tramadol, 83.0% in Turkey (31) and alfentanil, 51.5% in the United Kingdom (33). In this study, there was a preference for dexmedetomidine by 49.7% of respondents with a further 41.5% preferring morphine.

Respondents reported that weaning from ventilation was a challenge during analgesia management of patients. Morphine is a long acting opioid which if used for prolonged periods can accumulate. The altered pharmacokinetics of critically ill patients may alter drug metabolism and excretion and result in an increased duration of ventilation. Dexmedetomidine is a newer analgesic with sedative properties and has been shown to reduce the duration of mechanical ventilation, length of ICU stay and delirium (34, 35). Dexmedetomidine has been approved for up to twenty four hours for post-operative sedation after cardiac surgery, however its off-label use has increased as has its use in ICU. It is not recommended for routine use or as prophylaxis for delirium even in patients susceptible to delirium (34, 35). It is the most used sedative in private ICUs in this study.

The sedation assessment tools most commonly used include the Richmond Agitation-Sedation Scale (RASS) and the Ramsay Sedation Scale. The Ramsay Sedation Scale was initially developed to assess patient's level of sedation in ICU. The RASS (20) was published more recently than the Ramsay scale (36) and may be used to assess both the degree of agitation and sedation using a simple scale with either a positive or negative value (20). The RASS may be used more consistently by different observers for the same patient and it provides more

reproducible results. There were 41.5% of respondents who used the RASS and 38.3% who used the Ramsay scale in this study. The RASS was used by 61.0% of respondents in an international survey (28), as well as in studies in Spain, 84.9% (30), The People's Republic of China, 56.2% (29) and the United Kingdom, 64.7% (33). The Ramsay scale was the most used sedation scale in studies in Turkey, 57.5% (31) and India, 56.1% (32). The use of the RASS in this study is similar to its use in the aforementioned international survey, The People's Republic of China and India.

The most important factors influencing the choice of sedation was the patient's clinical diagnosis (74.6%) and the expected duration of ventilation (70.9%). The majority of respondents in this study (41.5%) used the analgesic drug morphine for sedation which may reflect the move toward "analgosedation" (5). It is, however, concerning that 31.1% of respondents still use midazolam despite the evidence for increased ventilator days or ICU stay (34, 37) and the recommendations for the use of sedatives for specific indications (7). Midazolam was used by the majority of respondents in studies in Turkey, 90.5% (31), Spain, 16.7% (30), The People's Republic of China 85.5% (29) and India, 95% (32). Dexmedetomidine was the preferred drug for sedation by 64.8% of respondents in this study. The difference in drugs most used and preferred may be associated with cost, off-label use and availability in each ICU. The use of midazolam in this study was higher than its use in studies in Spain, but less than its use in studies in Turkey, The People's Republic of China and India.

Most respondents in this study reported the high percentage of patients experiencing delirium as a challenge, which may be due to the high use of midazolam (27) and its associated risk for delirium when comparing benzodiazepines with non-benzodiazepine alternatives (34). Despite the concern for delirium, only 24.9% of respondents routinely assessed for delirium in this study. Delirium affects up to approximately 80% of mechanically ventilated patients (19). There were 40% of respondents who reported the assessment of delirium in an international survey (28). In studies in other countries, the assessment of delirium was reported by 50.5% in Turkey (31), by 81% in Spain (30), by 66.7% in The People's Republic of China (29), by 69.6% in the United

Kingdom (33) and by 34.4% in India (32). The routine assessment of delirium (24,9%) in this study was less than many international studies despite it being reported as a major challenge in ICU.

Non-pharmacological methods for analgesia and sedation were only used by 26.4% of respondents in this study. This limited use reflects the limited evidence for non-pharmacological methods (6, 7). The limited use is also reflected in international practice (28). Physical restraints were used by 94.8% of respondents in this study, with a protocol for physical restraint used by 53.6% and consent for restraint obtained by only 38.3%. The practice of physical restraints was evaluated in South Africa previously (38) and there is still a high use as reported by doctors in this study. A study in Spain reported that 14.2% of respondents used physical restraints (30). This study reports a much higher use of physical restraints when compared to the study in Spain.

A limitation to this study is that the results represent a description of reported practice from doctors at a single conference and not actual practice in all doctors in ICUs in South Africa. It is recommended that further in-depth research be done prospectively to evaluate the practice of analgesia and sedation in South African ICUs regarding socioeconomical circumstances.

Conclusion

This study presents a small window into the reported practice of analgesia and sedation in ICU in South Africa. Analgesia and sedation assessment are performed by most doctors, however, there is room for improvement of the assessment of delirium. Morphine is still commonly used, but the use of midazolam remains high despite evidence for its negative sequalae. The challenges of reducing ventilator days and reducing delirium in ICU may be addressed in future with improved training in assessment of patients, drug selection and the implementation of analgesia and sedation guidelines.

Conflict of interest

The authors declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

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Section 4: Proposal

Practice of analgesia and sedation in adult mechanically ventilated patients in South African ICUs

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4.1 Introduction and problem statement

Mechanical ventilation is used in critically ill patients requiring advanced organ support (1). Pain is experienced during mechanical ventilation or as a part of intensive care and therefore analgesics and sedatives are often provided for mechanically ventilated patients in the intensive care unit (ICU) (1). Effective management of pain forms a part of the overall sedation by decreasing agitation and distress (1). By effectively managing pain there may be a decreased need for the addition of sedative drugs during the patient's intensive care stay (2). However, in some patients, sedative drugs are indicated. Sedatives further improve patient comfort and allow patient-ventilator synchrony (3). Addressing pain and anxiety decreases the physiological and psychological stress response in critically ill patients (4). Mechanically ventilated patients may not be able to express themselves and may be in pain, distressed or delirious (5). Delirium affects 60 to 80% of mechanically ventilated patients (6). This incidence may be decreased with appropriate use of analgesia and sedation in ICU (7). Improving the quality of care and decreasing patient discomfort with the use of analgesia and sedation is based on drug choices and regimens, adequate means of assessment to understand the cause of pain or distress and an environment that reduces this stress (5, 8).

Pain is a major concern in the critically ill patient (9). Pain is often the most common memory during the patients ICU stay (10). An incorrect assessment of pain can result in the incorrect management of pain which can have physiological and psychological consequences in the critically ill patient. Validated pain scales may be used to assess patients and manage their pain. Pain scales such as visual analogue scales, numeric rating scales, behavioural pain scales and the critical-care pain observation tool may be used (11-14). The different pain scales may be used for patients able to report pain and those unable to report pain. Pain assessment is not routinely reported and may not form part of the analgesia protocol (5, 15).

Agitation can result in complications such as endotracheal tubes being dislodged or intravenous access being compromised. Sedation may decrease the work of

breathing of mechanically ventilated patients by improving ventilator synchronicity (3).

Non-pharmacological methods for analgesia and sedation include cybertherapy, massage, music therapy, limiting loud noise and limiting bright light. These work synergistically to improve patient comfort (16). Physical restraints are also used in the ICU setting as a form of mechanical sedation. This is complicated by legal and ethical factors for doctors and psychological trauma for patients. The prevalence of use of physical restraint remains high with insufficient guidelines regarding its use (17).

Sedatives are used to provide varying degrees of sedation and their use should be only when indicated and individualised to the patient (18, 19). Research describing the use of sedative drugs in general demonstrates that while sedatives are commonly used in ICU, no one sedative drug is better than the other (20). Evidence has emerged that sedation in the critically ill with prolonged use of certain drugs has a negative effect on patient outcomes (21-24) and has short and long-term consequences (7).

There is a shift towards lighter levels of sedation in ICU which can have a positive effect on patient outcomes (25). Drug choices to achieve sedation goals are important. For example, prolonged exposure to benzodiazepines may contribute to delirium in the critically ill, while the use of newer drugs such as dexmedetomidine may decrease this risk (26). Dexmedetomidine is one of the sedative-analgesic drugs and is an easily titratable drug that is increasingly used in ICU (27).

Several guidelines with recommendations for analgesia and sedation have been published such as those by the Society of Critical Care Medicine (7, 28), the European Society of Intensive Care Medicine (19) and the South African Society of Anaesthesiologists (18, 29).These guidelines define best practice strategies that may be used to optimise management of patients in ICU.

The use of analgesia and sedation varies between ICUs around the world (7). Analgesics which may be used in intensive care include drugs such as remifentanil, fentanyl, sufentanil, morphine and dexmedetomidine. Sedatives which may be used include midazolam, propofol and dexmedetomidine. Studies

which described the practice of analgesia and or sedation demonstrated a variety of analgesics used in different countries (30-36).

Analgesia and sedation management during mechanical ventilation plays an important role during the intensive care stay of critically ill patients (37). Analgesia and sedation practices are changing in response to the importance of pain, agitation and delirium in ICU (8, 25, 38). Optimised analgesic regimens together with sedation minimising strategies are increasingly used to decrease ventilation time, ICU stay and cognitive complications (38, 39). This is a shift to a more awake patient with improved mobility (40).

Although a study describing sedation practices in the context of delirium in ICU has been done as per personal communication via email correspondence with the authors, (Chetty, 08 March 2018) at the time of writing this proposal the results of this study had not been published. Analgesia and sedation are an evolving practice with new strategies emerging. A description of the practice of analgesia and sedation in South Africa is not known.

4.2 Aim and objectives

4.2.1 Aim

The aim of this study is to describe the practice of analgesia and sedation by doctors in adult mechanically ventilated patients in public and private ICUs in South Africa.

4.2.2 Objectives

The primary objectives of this study are to describe:

- assessment scales used for analgesia and sedation
- analgesia practices in mechanically ventilated patients
- sedation practices in mechanically ventilated patients
- non-pharmacological methods used for analgesia and sedation
- the factors that influence the choice of analgesics and sedatives.

The secondary objectives of this study are to compare the public versus private for the:

- use of an analgesia protocol
- use of a sedation protocol
- use of a delirium assessment

4.3 Research assumptions

The following definitions will be used in the study.

Intensivist: a specialist who has completed a sub-specialist qualification in critical care and is registered as such with the Health Professions Counsel of South Africa.

Non-intensivist: medical doctor or specialist without a sub-speciality in intensive care.

Adult: is a person who is 18 years and older.

The inclusion criterion in this study is doctors attending the annual 2018 Critical Care Society of Southern Africa (CCSSA) working in public and private ICUs.

The exclusion criteria are questionnaires that are more than 50% incomplete, essential information has been omitted, which includes demographics, analgesia and sedation assessment and drugs and or questionnaires that have not been completed by a doctor.

4.4 Demarcation of study field

The study will be conducted at the annual national CCSSA congress in Durban from 23 to 26 August 2018. On average, between 600 to 800 delegates attend the congress, of whom an estimated 60% are doctors.

Should the response rate be very low, additional data will be collected during the CCSSA refresher course in Johannesburg in November 2018 or via the online survey tool, Survey Monkey.

4.5 Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand. Provisional verbal permission for data collection was obtained from one of the co-chairs of the organising committee of the congress. Written formal permission will be requested from the president of the CCSSA and from both co-chairs of the CCSSA congress as well as the chair of the CCSSA refresher course (Appendix 1).

Delegates will be invited to participate and those who do will be given an information letter (Appendix 2) about the study. Completion of the self-administered questionnaire (Appendix 3) will imply consent. Anonymity will be ensured by requesting no identifying data. Questionnaires will be numbered for data collection purposes only. Questionnaires will be returned to a sealed data collection box at the CCSSA information desk. Only the researcher and supervisors will have access to the raw data, thereby ensuring confidentiality. Data will be stored securely in a locked cupboard for six years after completion of the study.

The study will be conducted according to the principles of the Declaration of Helsinki (41) and the South African Guidelines for Good Clinical Practice (42).

4.6 Research methodology

4.6.1 Research design

This study will use a descriptive, prospective, contextual study design.

A descriptive study is used to describe certain characteristics of a population or group as they occur naturally without interference from the researcher (43). This study describes the analgesia and sedation practices of doctors working in ICU.

A prospective study describes an outcome after observing a particular population group for a period of time (44). Data will be collected from doctors who are currently working in ICU. Data will be collected at the time the study takes place.

A contextual study describes a certain population group or a certain place. This group is referred to as a “small scale world” (45). This study will be performed amongst doctors working in South African ICUs.

4.6.2 Study population

The study population will consist of all doctors working in a public or private ICU in South Africa attending the annual 2018 CCSSA congress.

4.6.3 Study sample

Sample size

All doctors attending the congress will be invited to participate. The sample size will be realised by the response rate. A minimum of 60% of the doctors attending the congress will be considered an adequate response rate. Should there be a very low response rate, additional data will be collected from the CCSSA refresher course and possibly with the use of Survey Monkey.

Sampling method

A convenience sampling method will be used for this study. Convenience sampling is a non-random sampling method that involves “the choice of readily available participants or objects for the study” (44). This method of sampling uses a non-random sampling method (46). This study will collect data from doctors attending the CCSSA national congress.

Inclusion and exclusion criteria

The inclusion criterion in this study is doctors attending the annual 2018 CCSSA working in public and private ICUs.

The exclusion criteria are questionnaires that are more than 50% incomplete, essential information has been omitted and those that have not been completed by a doctor.

4.6.4 Data collection

Questionnaire development

A previously unpublished questionnaire by Chetty and Paruk was identified as appropriate for use and was adapted following a literature review. Permission to use and adapt the questionnaire was obtained from the authors (Appendix 4). This was adapted in consultation with three senior intensivists to ensure content and face validity.

The questionnaire (Appendix 3) will consist of the following information:

- participant demographics
- pain and sedation assessment
- analgesia practice
- sedation practice
- non-pharmacological analgesia and sedation practice
- factors influencing choice of analgesia and sedation.

Data collection

The organisers of the CCSSA national congress and possibly the CCSSA refresher course will be requested to advertise the study in between presentations with a slide requesting participation. Questionnaires will be distributed by the researcher during the congress.

The self-administered questionnaire (Appendix 3) contains an information letter (Appendix 2) which will be distributed to willing participants. The questionnaire will take approximately 15 minutes to complete. Participants will be requested to return the folded, completed questionnaire to a sealed collection box placed at the CCSSA information desk.

4.6.5 Data analysis

A Microsoft ® Office Excel spreadsheet will be used to capture the data. Data will be analysed with the assistance of a biostatistician using STATA version 15 (StataCorp, USA). Descriptive and inferential statistics will be used. Categorical

variables will be described using numbers and percentages. Categorical variables will be compared between the public and private sector using either Fishers exact tests or Chi squared tests. A p-value of <0.05 will be considered statistically significant.

4.7 Significance of the study

In critically ill patients, pain, agitation and delirium are a problem (8). Appropriate management of pain will decrease pain intensity (9). Analgesia and sedation practices have changed to improve patient outcomes (25, 38).

The practice of analgesia and sedation in ICU will be described. This will guide future education and training in ICU and allow emphasis to be placed on areas that need improvement. Critical areas in management may be identified to acquire new medication and to develop future protocols for management.

4.8 Validity and reliability of the study

The validity of a study describes the extent to which research truly measures what it sets out to measure and reliability represents the consistency of the measure achieved (47).

In this study validity and reliability will be ensured by the following measures:

- use of an appropriate research design
- use of a standardised questionnaire
- use of a questionnaire that has content and face validity
- data will be analysed in consultation of a biostatistician.

4.9 Potential limitations

Contextual studies assume that the sample population is representative of the population that is being described in the study (45). Doctors who attend congresses and refresher courses may be more up to date with current practices and guidelines.

The convenience sample may not represent all doctors working in ICU, as it will only include those individuals who attend the CCSSA congress and possibly the CCSSA refresher course or those who respond via survey monkey.

4.10 Project outline

4.10.1 Time frame

	2018								2019	
Activity	**Jan**	**Mar**	**April**	**May**	**Aug**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**
Proposal preparation										
Literature review										
Proposal submission										
Ethics approval										
Post graduate approval										
Data collection										
Analysis of results										
Write draft article										
Submission										

4.10.2 Budget

The Department of Anaesthesiology will bear the cost of printing and paper for the proposal, ethics and post graduate approvals. The remainder of the proposed research will be funded by the researcher, which includes airfare, accommodation and congress registration.

Should the response rate from the congress or refresher course not be adequate, the Survey Monkey tool will be used. The cost of using Survey Monkey will be approximately R4199 priced as a yearly cost.

Item	**Cost per item**	**Pages**	**Copies**	**Rand value**
Paper and printing	R1.00	3000		R3000
Binding	R200		3	R600.00
Total				R3600.00

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4.12 Appendices

Appendix 1: Permission letter to organisers of the CCSSA





Department of Anaesthesiology

University of the Witwatersrand

17 June 2018

Good day Prof Joubert, Dr Gopalan and Dr Wise

RE: Request for permission to collect data at The Critical Care Society of Southern Africa congress in Durban from 23 to 26 August 2018.

My name is Nicole Hendricks. I am a registrar in the Department of Anaesthesiology at the University of the Witwatersrand. I am studying towards my M Med degree. My research is entitled "Practice of analgesia and sedation in adult mechanically ventilated patients in South African ICUs".

My supervisor, Juan Scribante has made a telephonic request to Dr Gopalan regarding this research. I would now like to formally request permission to conduct my data collection at the CCSSA congress via a simple self-administered questionnaire.

I have attached my proposal that has been approved by the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the Faculty of Health Sciences. Your consideration is much appreciated.

Yours sincerely,

Nicole Hendricks

+27(0)73 449 3961

Supervisor	Juan Scribante
Co-Supervisor	Helen Perrie
Co-Supervisor	Carien Moller

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Appendix 2: Information letter

16 March 2018

The University of Witwatersrand

1 Jan Smuts Avenue, Braamfontein, Johannesburg, 2000

Dear Colleague

My name is Nicole Hendricks. I am a registrar in the Department of Anaesthesiology at the University of the Witwatersrand in Johannesburg. I am studying towards a Master of Medicine degree and I am required to complete a research project.

As part of my research I would like to invite you to participate in my study entitled "**Practice of analgesia and sedation in adult mechanically ventilated patients in South African ICUs**". The findings of this study may be used to identify the standard of practice by doctors. This will guide future education and training in ICU and allow emphasis to be placed on areas that need improvement. Critical areas in management may be identified to acquire new medication and to develop future protocols for management.

Should you agree to participate in this study, you will be asked to complete a self-administered questionnaire. No identifying information will be required and you will remain anonymous. There will be voluntary participation and consent is implied on completion of the questionnaire. You may withdraw your participation at any time. The study should take you no more than 15 minutes to complete. Whether completed or not, please place your questionnaire into the sealed box provided. Only my supervisors and I will have access to the raw data.

This study will be written up as a research report which will be available online through the university library website. If you have any queries or concerns regarding the ethical procedures of this study, you are welcome to contact the University Human Research Ethics Committee (Medical) of the University of the Witwatersrand. You may contact me on 073 449 3961 or the Chairperson of the HREC (medical), Prof C Penny on (011) 717 2301 or email Clement.penny@wits.ac.za. You may also contact the secretariat of the HREC (medical), Ms Z Ndlovu, Ms Mapula Maila and Mr Rhulani Mkansi on 011 717 1234/1252/2656/2700 or Zanele.ndlovu@wits.ac.za; Rhulani.mkansi@wits.ac.za; mapula.ramaila@wits.ac.za.

Thank you for your time.

Yours sincerely,

Dr Nicole Hendricks

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Supervisor

Dr Carien Moller

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Appendix 3: Questionnaire

Practice of analgesia and sedation in adult mechanically ventilated patients in South African ICUs

Please mark all answers with an X. All questions below refer to adult, mechanically ventilated patients.

Part 1. Participants demographics

1. Do you **manage** patients in the intensive care unit?

Yes	No

If no, please do not continue with this questionnaire.

2. Which of the following best describes your position?

Full time intensivist	Part-time intensivist	Specialist with an interest in critical care	Non-specialist doctor with an interest in critical care

3. What is your speciality?

Anaesthesiology	Internal medicine	General surgery	Paediatrics
Not applicable	**If other**, please specify _____		

4. What is your subspeciality?

Not applicable	Critical care	Pulmonology
If other, please specify_____		

5. Which sector are you mainly involved in?

Public	Private	Both

6. Approximately what percentage of your/your unit's patients require mechanical ventilation? _____%

Part 2. Monitoring and assessment of pain

7. Which policy or guideline are you using for pain and sedation in mechanically ventilated patients? (Please choose one of the following)

Local (hospital, personal)	Mixed local & international	Society of Critical Care Medicine – 2002	Society of Critical Care Medicine – 2013	Nil	I don't know
If other, please specify _____					

8. Does your unit have a written analgesia policy or protocol?

Yes	No

9. Do any of these factors play a role in the selection of agents for analgesia in mechanically ventilated patients?

Cost of the drug	Clinical diagnosis	Pharmacokinetics and pharmacodynamics of the drug
Familiarity	Availability in your ICU	Expected duration of ventilation
If other, please specify _____		

10. Which pain scale do you use?

Visual analogue scale	Numerical rating scale	Behavioural pain scale
Critical care pain observation tool	Don't know	Nil
If other, please specify _____		

11. How often do you use a pain scale? (Please choose one option for each ROW)

	Not at all	Not very often	Some of the time	Most of the time	All the time
When patient is first admitted					
Subsequent day shifts					
Subsequent night shifts					

12. Which would you say is your greatest challenge? Please mark as 1.
Please rank the remainder from 2 to 7
(2 = next biggest challenge. 7 = smallest challenge. 0 = Not a challenge)

	1	2	3	4	5	6	7	0
No uniform written guidance on analgesia protocol								
Compliance of your analgesia prescription for your patient from other members of the team								
Weaning patients off ventilation								
Ensuring compliance of analgesia protocol across ICU								
Limited choice of analgesic agents to use in ICU								
Need to reduce patient length of stay in ICU								

13. What analgesic would you **prefer** to use in mechanically ventilated patients?
For each row, rank according to preference **(1 = highest, 5 =least, 0= never)**

	1	2	3	4	5	0		
Morphine								
Fentanyl								
Sufentanil								
Alfentanil								
Remifentanil								
Dexmedetomidine								
Other, please specify _____								

14. Which analgesic agents do you **prescribe** in mechanically ventilated patients? **(1 = most prescribed, 6 = least prescribed, 0= not used)**								
Morphine	1	2	3	4	5	6	0	
Fentanyl								
Sufentanil								
Alfentanil								
Remifentanil								
Dexmedetomidine								
Other, please specify _____								

15. Approximately what percentage of mechanically ventilated patients receive more than one analgesic agent simultaneously? _____%

16. Do you use non-pharmacological strategies or techniques for analgesia and sedation?

Yes	No
If yes, please specify_____	

17. Do you use physical restraints in your patients?

Yes	No

18. Do you obtain consent for the use of physical restraints in your patients?

Yes	No

19. Do you have a physical restraint protocol?

Yes	No

Part 3. Monitoring and assessment of sedation

20. Does your unit follow a written sedation policy?

Yes	No

21. Do any of these factors play a role in the selection of agents for sedation in mechanically ventilated patients? Please mark all appropriate options.

Expected duration for ventilation	Pharmacokinetics and pharmacodynamics of the drug	Patients' clinical diagnosis
Familiarity	Availability	Cost
If other, please specify _____		

22. What level of sedation do you aim to keep majority of mechanically ventilated patients at?

Mild	Moderate	Heavy	Don't know	Nil sedation

23. Which sedation scale do you use?

Ramsey sedation scale	Richmond agitation sedation scale	Observer's assessment of alertness/sedation	ASA Sedation scale
Local scoring system, unspecified	Don't know	Nil	
If other, please specify _____			

24. How often do you use a sedation scale? (Please choose one option for each ROW)

	Not at all	Not very often	Some of the time	Most of the time	All the time
When patient is first admitted					
Subsequent day shifts					
Subsequent night shifts					

25. Which would you say is your greatest challenge? Please mark as 1.
Please rank the remainder from 2 to 7
(2 = next biggest challenge and 7 - smallest challenge. 0 = Not a challenge)

	1	2	3	4	5	6	7	0
No uniform written guidance on sedation protocol								
Compliance of your sedation prescription for your patient from other members of the team								
Weaning patients off mechanical ventilation								
Ensuring compliance of sedation protocol across ICU								
Limited choice of sedative agents to use in ICU								
Need to reduce patient length of stay in ICU								
High % of patients experiencing delirium								

26. What sedative would you **prefer** to use in mechanically ventilated patients?
For each row, rank according to preference **(1 = highest,5 =least, 0= never)**

	1	2	3	4	5	0		
Propofol								
Dexmedetomidine								
Remifentanil								
Midazolam								
Morphine								
Other (please specify) _____								

27. What is your sedative of choice for patients who are weaning off the ventilator?
For each row, rank according to use **(1 = highest,5 =least, 0= not use)**

	1	2	3	4	5	6	0	
Propofol								
Dexmedetomidine								
Remifentanil								
Midazolam								
Morphine								
Other (please specify) _____								

28. Which sedative agents you **prescribe** in mechanically ventilated patients?
(1 = most prescribed, 6 = least prescribed, 0= not used)?

	1	2	3	4	5	0		
Propofol								
Dexmedetomidine								
Remifentanil								
Midazolam								
Morphine								
Other (please specify)								

29. **Does your unit administer patient sedation holidays?** (Daily stopping of sedation. Sedation restarted once the patient is fully awake and obeying commands or until they require sedation)

Yes	No	Sometimes

30. Approximately what percentage of your patients are on sedation? _____%

31. Do you routinely perform delirium assessments on your ICU patients under sedation?

Yes	No	Sometimes

32. Do you see a need to change your methods concerning analgesia and sedation?

Yes	No

33. If yes, the main reason would be?

Current publications	New guidelines	Expert opinion
Availability of drugs	Costs	
If other, please specify _____		

34. Which of the following do you think would benefit your unit to receive additional support or training for? Rank in order of importance
(1= most important and 8 = least important. 0= not required)

	1	2	3	4	5	0		
Greater choice of analgesic agents?								
Greater choice of sedative agents to achieve sedation goals?								
Reduced complication from sedation								
Assessment of pain								
Assessment of agitation								
Establishment of delirium assessment criteria								
Reducing ventilator days after prolonged infusions of drugs								
Earlier mobilization and exercise of patients								
Written protocols in the unit								
Ensuring compliance when applying the unit's protocols								

Thank you for taking the time to complete this questionnaire.

Appendix 4: Permission for use and adaptation of questionnaire

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

Good day Dr Chetty and Prof. Paruk

My name is Nicole Hendricks. I am a registrar in the Department of Anaesthesia at the University of the Witwatersrand. I am studying towards my M Med.
My research is entitled "**Practice of analgesia and sedation in adult mechanically ventilated patients in South African ICUs**". The findings of this study may be used to identify the standard of practice by doctors. This will guide future education and training in ICU and allow emphasis to be placed on areas that may need improvement. Critical areas in this management may be identified to acquire new medication and to develop future protocols for management.

My objectives will include:

- assessment scales used for analgesia and sedation
- analgesia practices in mechanically ventilated patients
- sedation practices in mechanically ventilated patients
- non-pharmacological methods used for analgesia and sedation
- the factors that influence the choice of analgesics and sedatives.

I acknowledge that you have both completed a study describing delirium in ICU and the results will be published at a later stage.

I would like to request permission to use the survey questionnaire from your study and if necessary, to modify it to meet my objectives.

Thank you for any consideration to my request. I am happy to send any further information as required.

Your assistance will be appreciated.

Kind regards,
Dr Nicole Hendricks
Nicole.hendricksmd@yahoo.com
Cell: 073 449 3961

Provisional verbal permission for use and adaptation of the questionnaire was obtained from both Dr S Chetty and Prof F Paruk. Formal written permission has been requested.

Below: Email correspondence:

Sean Chetty <seanchetty@gmail.com>
To: Nicole Hendricks
Cc: FATHIMA PARUK
Mar 7 at 12:58 PM
Dear Dr Hendricks

Thanks for the e-mail.

In principle I am very happy for you to use the same questionnaire that we used in our study. However, I was not the sole author on the study and I am copying Professor Paruk, who was the senior author on this study, on my reply. She will also have to give approval.

Kind Regards
Sean
Dr Sean Chetty | MBChB(Natal) DCH(SA) DA(SA) FCA(SA) Cert.Crit.Care(SA) PhD
Head: Clinical Department and Deputy Head of Department
Department of Anaesthesiology and Critical Care
Faculty of Medicine and Health Sciences

e: seanchetty@gmail.com| t: +27 21 938 9230
m: 083 707 4444 | f**:** +27 0866 170 530
a: Room 2042 | **Clinical** Building | Francie van Zijl Drive | Tygerberg | Cape Town | South Africa

Juan Scribante <Juan.Scribante@wits.ac.za>
To: Sean Chetty
Cc: Fathima Paruk,Helen Perrie,nicole.hendricksmd@yahoo.com
Mar 8 at 11:58 AM
Good morning Sean and Fathima
Thank you for agreeing that Nicole can use and adapt if necessary your questionnaire for her M Med. Sean I have just spoken to Fathima and she has agreed telephonically. Unfortunately, she was at the airport at the time and the questionnaire is on an old computer at home. Due to time constraints we are very desperate for the questionnaire, Sean would you be so kind to please forward to us.
Kind regards, Juan Scribante

Section 5: Annexures

5.1 Ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Nicole Hendricks et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180417

NAME: (Principal Investigator)	Dr Nicole Hendricks et al
DEPARTMENT:	Anaesthesiology The annual national Critical Care Society of Southern African Congress (CCSSA) in Durban ICC
PROJECT TITLE:	Practice of analgesia and sedation in adult mechanically ventilated patients in South African ICUs
DATE CONSIDERED:	04/05/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Juan Scribante
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/07/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **April** and will therefore be due in the month of **April** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

5.2 Graduate studies approval

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

12 June 2018
Person No: 0212359V
PAG

Dr NE Hendricks
Postnet Suite 210
Private Bag X2600
Houghton
Johannesburg
2041
South Africa

Dear Dr Hendricks

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Practice of analgesia and sedation in adult mechanically ventilated patients in South African ICUs* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.3 Permission letter from organisers of the CCSSA

Dean Gopalan <gopalan@ukzn.ac.za>
To: Nicole Hendricks,ivan.joubert@uct.ac.za,robertwise@webafrica.org.za
Cc: Juan Scribante,Helen Perrie,Carien Moller,Nevi Letcher
06 Jul 2018 at 09:37

Dear Dr Hendricks

We discussed your request at our meeting yesterday and are happy to allow you to conduct your research at the conference.

I have cc'd Nevi Letcher, our PCO, with whom you may communicate further to facilitate this.

Kind regards

Dean Gopalan Head: Discipline of Anaesthesiology & Critical Care,
Clinical Medicine|College of Health Sciences
T: +27 312604328; **E**: Gopalan@ukzn.ac.za
A: Room 420, 4th Floor Main Building, Nelson R Mandela School of Medicine Campus, 719 Umbilo Road, Durban.
W: anaesthetics.ukzn.ac.za

From: Nicole Hendricks <nicole.hendricksmd@yahoo.com>
Date: Monday, 25 June 2018 at 15:50
To: "ivan.joubert@uct.ac.za" <ivan.joubert@uct.ac.za>, Dean Gopalan <Gopalan@ukzn.ac.za>, "robertwise@webafrica.org.za" <robertwise@webafrica.org.za>
Cc: Juan Scribante <juan@scribante.co.za>, Helen Perrie <helen.perrie@wits.ac.za>, Carien Moller <carien.moller@gmail.com>
Subject: RE: Data collection for MMED at the CCSSA

Good day,

RE: Data collection for MMED at the CCSSA in Durban in August 2018.

My name is Nicole Hendricks. I am a registrar in Anaesthesia and I am currently doing my MMED. My supervisor, Juan Scribante had previously requested telephonic permission for data collection for this MMED at your congress this year.

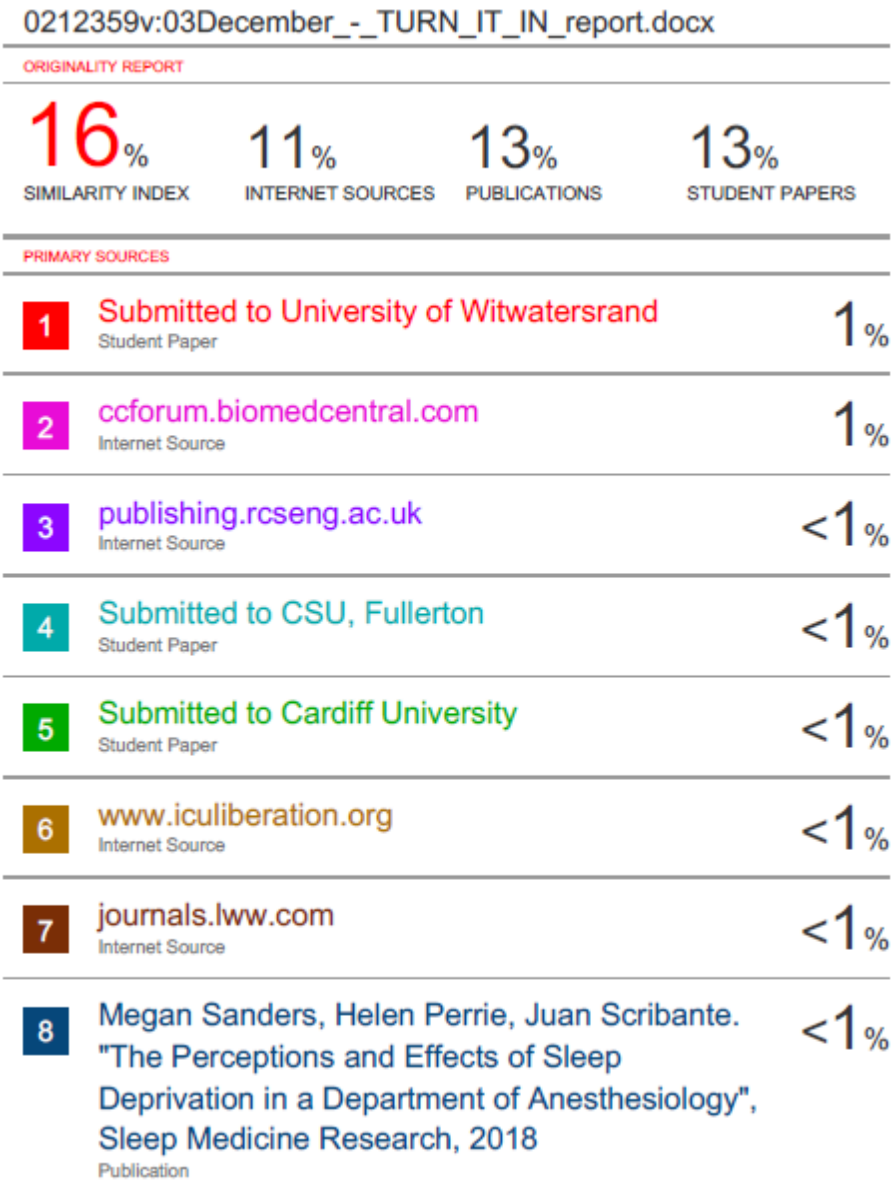
At the advice of the chair, I have now attached a formal permission request together with my proposal. Your consideration is greatly appreciated.

Thank you very much.

Kind regards,

N Hendricks

5.4 Turnitin report



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