The association of duration of mechanical ventilation and ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2015 versus 2017, a retrospective cohort analysis.

By

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Submitted in fulfilment of the requirements for the degree

MAGISTER MEDICINAE (ANAESTHESIOLOGY)

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November 2019

Declaration of authorship

I, Reinier Swart, hereby declare that the mini-dissertation titled **"The association of duration of mechanical ventilation and ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2015 versus 2017, a retrospective cohort analysis"** submitted by me, in fulfilment of the requirements of the coursework **Magister Medicinae (Anaesthesiology)** degree, is based on actual and original work carried out by me. Any references to work done by any other person or institution or any material obtained from other sources have been duly cited and referenced.
I further certify that the research paper has not been published or submitted for publication or in fulfilment of other degree requirements anywhere else.

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Acknowledgements

For those who made this mini-dissertation possible, I would like to pay special thanks to the following individuals:

My supervisors, Dr SD Maasdorp and Prof. G Lamacraft, for their support and the countless hours spent reading my handiwork.

Prof. G Joubert, Department of Biostatistics, thank you again for the many hours spent looking at my numbers and helping me and others to make sense of our past practices.

Matron G Joubert, I would like to thank you for running hither and thither with all the heavy boxes and helping me to gather all the information of the patients who helped us to generate this valuable data.

Dedication

This mini-dissertation is dedicated to all the friends and family who stood by me during the times when I could not be there for them. Through all the hardships and joy that we wanted to share, but could not as a result of my endeavours. I love you all even though I was not always there to express it.

Most of all I want to humbly dedicate this work to my loving and resilient wife, Eleanor Bron-Swart, who endured my silent presence, longing absence and the times when my words did not convey my utter awe for your unwavering support.

Reinier

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Abstract

Background: Sedation is often used in the intensive care unit (ICU), but can be harmful if used inappropriately or excessively. Dexmedetomidine offers a favourable, co-operative sedation profile, despite a higher relative cost compared to other commonly used sedatives. Dexmedetomidine also has analgesic and opioid-sparing properties. It is, however, highly protein-bound with known haemodynamic side effects, such as bradycardia and hypertension. The multidisciplinary ICU at our central South African hospital adopted the use of dexmedetomidine over the period of 2016. This study was done to see whether this change in practice affected the ICU length of stay and duration of mechanical ventilation at this unit.

Methods: This study was done as a retrospective cohort analysis and the files of patients who were sedated with midazolam and propofol in 2015 and those who were sedated with dexmedetomidine in 2017, were used to note the sedatives, demographic data, vital data and treatment. Institutional Ethics (UFS-HSD2018/0542/2808) and Free State Department of Health approval was obtained. Funding was obtained from the Research Committee of the Three Schools of Medicine, UFS to secure a research assistant who helped with collecting file numbers and files. Group 2015 and Group 2017 were also analysed for possible confounders, where appropriate, and these confounders were excluded for a re-analysis to assess for contribution to the primary or secondary outcomes.

Results: There were 52 patients in Group 2015 and 60 patients in Group 2017. No difference was found in the duration of ICU length of stay (LOS) (median 5 vs 8.5 days, $p = 0.1$) or mechanical ventilation (median 91 vs 129 hours, $p = 0.44$). Those who were sedated with dexmedetomidine had better initial prognoses (median APACHE II 13 vs 18), were sedated for greater fractions of their total ICU admission times (median 46% vs 25%) and had a higher incidence of hypotension and bradycardia (36.7% vs 11.4%, $p < 0.01$); which did not relate to a higher mortality. The findings of more incidences of hypotension may relate to the bradycardia experienced with the use of dexmedetomidine. Spearman rank correlation coefficients also showed a weak to moderate association with longer ICU stay and ventilation duration when the duration of sedation with midazolam or propofol was shorter.

Conclusion: This study did not show a reduction in ICU LOS or mechanical ventilation with the advent of dexmedetomidine in our unit. The absence of regular documentation of sedation levels and scheduled sedation breaks may have contributed to these results. Dexmedetomidine has a role to play in the ICU setting, but it should only be used when clearly indicated, with a clear protocol for its use, in order to warrant its higher cost. Vigilance for hypotension and bradycardia is required when using dexmedetomidine. More prospective research is required to validate these findings in a resource-constrained environment, but evidence from high income countries supports these findings.

Keywords

Death

Dexmedetomidine

Discharge

Duration of mechanical ventilation

Intensive care unit / ICU

Length of stay / LOS

Midazolam

Propofol

Sole or adjuvant

Sedative

List of acronyms and abbreviations

APACHE	-	Acute Physiology and Chronic Health Evaluation
BIS	-	Bispectral Index
bpm	-	Beats per minute
FSDOH	-	Free State Department of Health
GABA	-	Gamma Aminobutyric Acid
g/L	-	Grams per litre
HOD	-	Head of Department
HSREC	-	Health Sciences Research Ethics Committee
IASP	-	International Association for the Study of Pain
ICS	-	Intensive Care Society
ICU	-	Intensive Care Unit
IV	-	Intravenous
Ivi	-	Intravenous infusion
LOS	-	Length of Stay
mcg/kg/min	-	Micrograms per kilogram per minute
mcg/kg	-	Micrograms per kilogram
µmol/L	-	Micromol per litre
mmHg	-	Millimeters of mercury
RASS	-	Richmond Agitation Sedation Scale
RCT	-	Randomised Controlled Trial
SAS	-	Sedation-Agitation-Scale
SCCM	-	Society of Critical Care Medicine

List of appendices

Chapter 1: Introduction, background and literature review

1.1 The purpose of sedation in the intensive care unit

Sedation in the critical care unit is commonplace. The most frequent recollection of a patient's Intensive care unit (ICU) stay is pain(1) and this "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International association for the study of pain / IASP definition of "pain")(2) is often associated with agitation resulting in the accidental removal or disconnection of vital equipment and infusion lines.

At follow-up interview many patients who were admitted to the ICU report delusional recollections; when they cannot recall specific facts of their ICU stay, nightmares and feelings of loss of control are often all they can remember.(3) One has to remember that sedation does not mean a patient is pain-free and analgesia is probably more important in the critical care setting.(4) Patients in pain and discomfort may become agitated and ameliorating the precipitants is all that is often needed to calm a patient instead of applying inappropriate pharmacological or mechanical restraints.(3)

A principal aim of sedation is to render a patient co-operative or unaware in an artificial environment which is possibly very stimulating to the patient (the intensive care unit). This can lead to agitation and delirium - which are associated with worse morbidity and mortality (in up to 27% of mechanically ventilated patients).(5,6) Thanks to newer ventilators and ventilator modes, ventilator dyssynchrony is a less common occurrence, but sedation is often required for other reasons (see table I).(1)

Table I – Indications for sedation in ICU*(1)*

- Physiological difficulty in ventilation
- Difficulty in oxygenation
- Ventilator dyssynchrony (mechanical difficulty in ventilation)
- Neuroprotection
- Severe pain (e.g. lactrodectism, polytrauma or dressing changes in burns)
- Refractory status epilepticus
- Severe neuromuscular diseases (e.g. Guillain-Barre)

1.2 Sedation practices in the intensive care unit

The term sedation is often interpreted to include the spectrum of anxiolysis to deep procedural sedation, where patients do not move during deeply painful stimuli.(7) As a result, it is important that the desired level of sedation be clearly defined during sedation. Many sedation scales have been developed to this end. Probably the most widely used scale is the Richmond Agitation Sedation Scale (RASS) and a score of +1 to -2 is often aimed for. An example of the RASS is found in table II.(3)

Table II – Richmond Agitation Sedation Scale		
Score	**Term**	**Description**
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Other commonly used scales are the Ramsay score, sedation-agitation-scale (SAS) and Comfort scale, among others. For fear of inaccuracy due to subjectivity and to avoid the possibility of oversedation, or as a result of long assessment intervals, other more physiologically based ways have been proposed to monitor sedation in the ICU, such as the use of processed EEG monitors.(3,8)

Sedation may be harmful when used inappropriately and may, contrary to the healthcare provider's intention, lead to longer ICU stay and mechanical ventilation, which is why sedation practice should be targeted. It has also been proven that early deep sedation leads to longer times to extubation and higher 180 day mortality rates.(9) It is therefore a requirement to assess the level of a patient's sedation frequently and provide regular, scheduled sedation breaks (which are also associated with lower total sedative dosages).(1,10–12)

Sedation is not always necessary and ancillary methods at addressing the cause of agitation are often effective in patients where deep sedation is not a requirement (eg deep sedation is needed in patients who require a reduction of their cerebral metabolic rate). In fact, seeing to a patient's daily feeding and hydration requirements may go a long way towards avoiding unnecessary sedation.(10) The Society for Critical Care Medicine (SCCM) has released the ABCDEF bundle for the assessment, prevention and management of sedation and delirium in the ICU.(13) This approach encompasses the following important tenets:

- Assess for, prevent and manage pain early and effectively
- Both awakening and spontaneous breathing (implemented daily) should be common practice
- Choice and targeting of sedation levels (for example deeper levels in patients with raised intracranial pressure and lighter levels in other patients)

- Delirium monitoring on a regular basis with appropriate management once identified (which includes nonpharmacological techniques initially and then dexmedetomidine once the agitated phenotype of delirium is identified)(13–15)
- Early mobilisation and exercise (although there is not enough evidence to support this intervention in decreasing the incidence of delirium according to a recent Cochrane review, it may decrease the incidence of sarcopaenia and have other health benefits)(16)
- Family engagement in the recovery process of the ICU patient

The ABCDEF bundle has been validated by Pun *et al* (2018) in over 15 000 patients to reduce the incidence of death within the first 7 days, next-day mechanical ventilation, coma, delirium, physical restraint use, ICU readmission, and discharge to a facility other than home.(17)

Strøm *et al* (2010) described the benefits of analgosedation in 2010 for the first time. It was shown that morphine only (as compared to morphine and sedation) reduced ventilated days.(4) On closer inspection, though, the morphine only group in Strøm's study did receive occasional sedation, but his findings have been validated over time.(3)

1.3 Commonly used sedatives in the intensive care unit

The choice of sedative may often be as important as the dosage used and the lightest level of sedation that is possible and practicable should generally be targeted. One randomised controlled trial showed that lighter levels of sedation were associated with shorter ICU stay and duration of mechanical ventilation versus deeper sedation.(18) Many trials have been conducted in an attempt to prove the superiority of one sedative over another and none has yet proven to be superior in large, randomised studies.(1) The Intensive Care Society does, however, recommend non-benzodiazepine strategies over benzodiazepine strategies, but this recommendation has not permeated to all units.(3) A few examples of commonly used sedatives are presented in table III.

Table III – Sedatives often used in ICU(19)

Hypnotics – Ketamine, Propofol, Thiopentone
Benzodiazepines – Midazolam
Tranquilisers – Haloperidol
Opioids – Morphine, Fentanyl
Alpha 2 agonists – dexmedetomidine, clonidine

The pharmacodynamic profile of each of the currently available sedative drugs falls short of the complete list of properties that would be required of the "ideal sedative"

(table IV). This requires tailoring of the sedative strategy to the individual patient, based on their pharmacological requirements and physiological status quo.(3,8)

Table IV – Properties of the ideal sedative(19)

- Pharmaceutics
  - Ease of administration
  - Does not promote growth of pathogens
  - Easily prepared and long shelf life
- Pharmacodynamics
  - Predictable dose-dependent effects with minimal individual variation
  - Provides appropriate sedation, anxiolysis, amnesia and analgesia
  - No tolerance and withdrawal symptoms
  - Provides facilitation of ventilator synchrony and the performance of various procedures and nursing interventions
- Pharmacokinetics
  - Rapid onset of action
  - Easily titratable level of adequate sedation
  - Short-acting, allowing patient assessment, rapid recovery following discontinuation, easy weaning from mechanical ventilation, and early extubation
  - Minimal metabolism; not dependent on normal hepatic, renal, or pulmonary function
  - No active or toxic metabolites
  - Safe for all ages with no age-related changes in pharmacokinetics
  - Lack of accumulation with prolonged administration
- Interactions
  - No or minimal interactions with other drugs
- No or few adverse effects
  - No anaphylaxis or allergic reaction
  - No nausea, vomiting, or phlebitis
  - Minimal respiratory depression
  - Minimal effect on cardiovascular function
  - No pain on injection
  - No suppression of cortisol production by the adrenal cortex
- Other
  - Cost effective
  - Lack of abuse potential
  - Widely available

1.3.1 Dexmedetomidine

Dexmedetomidine is often used either as a primary sedative, or when others have failed in ICU due to the theory that it causes co-operative sedation.(20) Dexmedetomidine also has analgesic and opioid-sparing effects through its agonism of alpha 2C-adrenergic receptors in the central nervous system.(20)

This has led to several small studies which investigated the possible superiority of dexmedetomidine over other conventional ICU sedatives. Dexmedetomidine seems

to have benefits over midazolam with regards to mechanical ventilation, but at the risk of added side effects.(21,22) Due to this evidence, it was postulated that dexmedetomidine would perform superiorly when compared head-to-head with other sedatives in a randomised controlled trial, but the SPICE III trial did not substantiate this belief. It was found, however, that when dexmedetomidine was used as a sole sedative, it was not associated with a better 90 day survival in patients expected to be ventilated for longer than a 'calendar day', as per study criteria, and additional sedation was more often required to achieve prestated sedation targets.(23) Once agitated delirium has been diagnosed, though, dexmedetomidine has been shown to decrease the duration of ventilation.(22)

The pharmacological properties of dexmedetomidine (as an ICU sedative) are listed in table V.(20)

Table V – Pharmacological properties of Dexmedetomidine

Dose:	Loading: 1mcg/kg ivi over 10 – 30 minutes Maintenance: 0.2 – 0.7 mcg/kg/hour
Contraindications:	- Compromised critically ill patients - Heart block Caution in: - Concomitant neuraxial anaesthesia
Adverse effects:	- Prolonged infusions may lead to drug accumulation, emergence delirium, dependence and withdrawal phenomena. - Adrenal steroid production may be inhibited. - Inhibition of insulin secretion. - Initial hypertension (especially with a loading dose), followed by hypotension and bradycardia. - Nausea and dry mouth. - May potentiate respiratory depression of other analgesics and sedatives.
Pharmacodynamics:	Alpha 2-adrenergic agonist – meaning it causes presynaptic auto-inhibition of the autonomic nervous system. Different types of alpha 2 receptors are located throughout the body allowing for analgesia, central sympatholysis, neuroprotection and altered cognition.
Pharmacokinetics:	Dexmedetomidine is primarily administered as an intravenous (IV) infusion during ICU sedation. Its onset of action is 15 minutes. Dexmedetomidine's beta half-life is around 2 hours, meaning that it would take approximately 8 to 10 hours to achieve steady state (and this is why a loading dose is essential, but could be detrimental to the critically ill patient if their physiology is too unstable as can lead to hypotension or reduced cardiac output).

	Context-sensitive half-time is estimated at 20 – 30 minutes. The drug is 94% protein-bound to albumin and alpha1-acid glycoprotein (downward dosage adjustments are required in patients with low serum albumin levels). It is extensively metabolised in the liver by the cytochrome p450 enzyme system (quadrupling beta half-life in liver failure, and therefore requiring a decrease in maintenance dose; it also has several drug interactions with other drugs metabolised by this system, and may potentiate the effects of other concomitantly administered sedatives) and is 95% excreted in the kidney (requiring dose adjustment in renal failure).

The achievement of a more preferable quality of sedation is one of the reasons for clinicians preferring dexmedetomidine over other sedative agents.(3,9) Patients are often able to perform psychomotor tasks adequately on awakening and when given an instruction during dexmedetomidine sedation, therefore the preference.(24)

It is, however, evident from table V that dexmedetomidine is not a cardiovascularly inert drug and reinforces the point that the prescription of sedative agents should be individualised rather than routinely prescribing one agent over another. Dexmedetomidine has been associated with a significant incidence of bradycardia and the impact it may have on cardiac output in the setting of haemodynamically labile patients may also affect the utility of this drug in certain patient groups.(25)

1.3.2 Benzodiazepines

Table VI – Pharmacological properties of Midazolam

Dose:	0.25 – 1mcg/kg/min
Contraindications:	Caution in: - The elderly - Co-administration of other sedatives or opioids as cardiovascular stability may be lost
Adverse effects:	- Respiratory depression - Paradoxical agitation at low dosages - Due to amnestic effects, some patients may have dysphoric recollection of the sedation period - May cause cardiovascular suppression when administered with other sedatives or opioids
Pharmacodynamics:	$GABA_A$-agonist – potentiates the binding of GABA to its receptor site and thereby increasing chloride influx and neuronal membrane hyperpolarisation.

Pharmacokinetics:	- Peak effect 2 – 3 minutes (IV) - 96 – 99% plasma protein binding - Extensively metabolised in the liver by CYP3A4 and CYP3A5 - Phase I metabolites are active and are excreted by the kidneys (thus they may accumulate in renal failure) - High interindividual variability in metabolism (thus unpredictable pharmacokinetics) - Context-sensitive half-time of 3-15 hours (residual sedation may be effective during sedation breaks, thus worsening outcomes)

The use of midazolam (table VI) as a first-line sedative agent for prolonged use in the ICU has recently been discouraged, with Zaal *et al* (2015) showing that the deliriogenic effects of midazolam are dose dependent and are more prevalent with continuous infusions.(26) Two randomised controlled trials showed that midazolam was associated with both a higher incidence as well as a longer duration of delirium when compared to dexmedetomidine.(21,27,28) Lorazepam was also proven to increase the total duration of coma and delirium in the MENDS study when compared to dexmedetomidine as a sedative in ICU.(29) It is due to this resounding agreement of the evidence that benzodiazepines are not recommended by by the Intensive Care Society (ICS) nor the SCCM as first line sedatives.(3,8)

Despite the condemnation of the use of benzodiazepines for sedation in ICU, their relative haemodynamic stability when compared to propofol, and the significantly lower cost of these drugs as compared to dexmedetomidine, give them a significant advantage in resource-constrained environments. Benzodiazepines also have some specific indications, such as benzodiazepine withdrawal, delirium tremens and cocaine intoxication, among others, and as a result these drugs will likely not disappear from the armamentarium of the modern intensive care unit.(20)

1.3.3 Propofol

After the registration of 2,6-diisopropylphenol (propofol) in Europe in 1986 this drug quickly gained popularity as a general anaesthetic and sedative (due to its titratability).(30) Propofol also has other favourable effects such as being an antiemetic, anticonvulsant and an effective drug for the reduction of the cerebral metabolic rate (see table VII).(20) It is important to note that, as with any drug, propofol is not without its risks. Propofol is a potent vasodilator with negative inotropic and chronotropic effects. It is also associated with propofol-related infusion syndrome, especially when it is given in excess of 4mg/kg/hr for over 48hours. In critically ill children, and more so in sepsis, this phenomenon of cardiac failure, lipaemia and uncoupling of the electron transfer chain in the generation of energy-rich substrates may be seen at even lower doses per kilogram.(3,20)

Table VII – Pharmacological properties of Propofol

Dose:	25 – 75 mcg/kg/min
Contraindications:	- Hypovolaemia - Hypotension - Cardiac compromise Caution in: - High doses (>5mg/kg/hour) for periods more than 48 hours - Critically ill with energy depletion - Critically ill children - Severe head injury
Adverse effects:	- Hypotension - Myocardial depression - Emulsion emboli - Propofol infusion syndrome - Pancreatitis - Hyperlipidaemia
Pharmacodynamics:	- Prolong the binding of GABA to its receptor - Blocks central nicotinergic receptors
Pharmacokinetics:	- Onset of action 30 seconds - Time to peak effect after a bolus is 90 – 100 seconds - Alpha half-life is 2 – 4 minutes and beta half-life is 30 – 60 minutes - Final elimination is 4 – 23 hours (due to its highly fat-soluble nature) - Context sensitive half-time of less than 40 minutes after 8 hours - Highly protein-bound (99%)

When compared to midazolam, propofol has been shown to reach sedation targets earlier with faster recovery after cessation of the infusions.(31) Dexmedetomidine has also been shown to be non-inferior to propofol with regards to the incidence of delirium, duration of mechanical ventilation and length of ICU stay.(21,27)

1.3.4 Antipsychotics

Despite the lack of evidence of efficacy, haloperidol is commonly prescribed to agitated patients in the ICU. A recent randomized controlled trial has however failed to show that the use of typical or atypical antipsychotics are superior to placebo in reducing the duration of either hyperactive or hypoactive delirum.(32)

The SCCM's 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU also does not support the use of haloperidol in the setting of established delirium. The practice of administering typical and atypical antipsychotics in this setting should probably be abandoned until more studies are conducted.(8)

1.4 Motivation for and potential implications of studying sedation practice at Universitas Academic Hospital's ICU's

Since 2015 there has been a 903% increase in the issuing of dexmedetomidine by the pharmacy at the Universitas Academic Hospital in Bloemfontein (largely attributed to its use in the multidisciplinary ICU). There has not been a proportionate expansion of treatment capacity.This suggests that there has been an increased preference for the use of dexmedetomidine despite the absence of literature indicating its superiority in many circumstances and despite its greater cost to the hospital.(10) The cost to the hospital as at 11 May 2018 per ampoule of dexmedetomidine (200mcg/2ml) was R440.3295. When contrasted with the cost of midazolam (R3.69 for a 5mg/3ml ampoule – and propofol – R46.15 for a 500mg/50ml ampoule) the cost of dexmedetomidine indicates a possibly significant financial burden to the hospital.(33)

Although the relative increase in cost seems daunting (a more than 110 fold increase in cost when compared to midazolam, with a sudden surge in usage of 903% from the start of 2015); the absolute increase in cost (from R3.69 per ampoule of midazolam as compared to R440.3295 for dexmedetomidine) may not be significant if this could be offset by the saving of even one day's admission to the ICU as shown in table VIII.

Table VIII – Cost implications of sedatives vs one day in ICU(33,34)

- One ampoule of midazolam 5 mg / 3 ml – R3.69
- One vial of propofol 500 mg / 50ml – R46.15
- One vial of dexmedetomidine 200 µg / 2 ml – R440.33
- One day's stay in ICU (consumables not included) – R10 158

This sudden increase in the usage of dexmedetomidine may also be contributed to by other departments, such as anaesthesiology, but tracking the paper trail of each ampoule is difficult. The difficulty arises when ampoules are redispensed to other units to meet their demands, making initial dispensing numbers unreliable. The drug control books of the multidisciplinary ICU, however, did show a marked increase in the dispensing of dexmedetomidine ampoules in alignment with the increased dispensing by the pharmacy over the same period of time.

1.5 Aim of the study

The aim of this study was to determine if the preferred use of dexmedetomidine at the Multidisciplinary ICU at Universitas Academic Hospital was associated with a shorter duration of mechanical ventilation and / or a reduced length of stay in the ICU.

1.6 Objectives of the study

This study attempted to identify the potentially resource-sparing benefits of using dexmedetomidine (in contrast to midazolam and / or propofol) by looking at the following parameters:

Primary objectives:

- To determine whether the use of dexmedetomidine in 2017, as compared to other sedatives in 2015, had an impact on:
    - Duration of mechanical ventilation (hours)
    - Length of ICU stay (hours)

Secondary objectives:

- To determine whether dexmedetomidine affected the incidence of adverse events during sedation (as are identifiable during a retrospective document review) by looking at blood pressure and heart rate measurements during sedation to identify:
    - Hypotensive incidents (which were defined as any recorded systolic blood pressure less than 90 mmHg or any mean blood pressure less than 65 mmHg by the multidisciplinary ICU protocols)
    - Bradycardia (which was defined as any heart rate less than 60 bpm)
- To determine if the severity of illness influenced the primary objectives (by dividing patients into prognostic strata according to their APACHE II scores)To determine if the patients' habitus may have influenced the primary objectivs by recording their estimated weights
- To determine whether the relative fraction of time sedated when compared to either ICU stay or ventilation duration was different or could have influenced the primary or secondary objectives
- To determine whether the patients' means of the upper and lower values of serum creatinine or the means of the upper and lower values of serum albumin may have been significantly different
- To determine whether the patients' final outcomes (death or discharge) may have differed between the cohorts

The sedation practices of 2015 were contrasted with the patients that were administered dexmedetomidine in 2017. The reason these two years were being contrasted to one another is the fact that dexmedetomidine was gradually introduced into practice in this unit during 2016. Therefore, individual consultants slowly began using the drug and 2016 was excluded to prevent the selection bias that may have occurred due to this gradual change in practice from affecting the results.

1.7 Hypothesis

It was hypothesized that dexmedetomidine as a single or adjuvant sedative agent would not be associated with a reduced length of ICU stay or duration of mechanical ventilation compared to alternative sedative agents. Statistical significance was accepted as a null hypothesis of more than five percent.

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Chapter 2: Publishable manuscript

Title: **The association between dexmedetomidine as a single or adjuvant sedative versus other sedatives and the duration of mechanical ventilation and ICU stay in critically ill patients in a central South African ICU.**

Keywords: Dexmedetomidine, Propofol, Midazolam, ICU / Intensive care unit, Sedation, Duration of ventilation, LOS / Length of stay

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Abstract

Background: Sedation is often used in the intensive care unit (ICU), but can be harmful if used inappropriately or excessively. Dexmedetomidine offers a favourable, co-operative sedation profile, despite a higher relative cost. It also has analgesic and opioid-sparing properties. It is however highly protein-bound with known haemodynamic side effects, such as bradycardia. The multidisciplinary ICU at our central South African hospital adopted the use of dexmedetomidine over the period of 2016. This study was done to see whether this change in practice affected the ICU length of stay and duration of mechanical ventilation at this unit.

Methods: This study was done as a retrospective cohort analysis and the files of patients who were sedated with midazolam and propofol in 2015 and those who were sedated with dexmedetomidine in 2017, were used to note the sedatives, demographic data, vital data and treatment. Group 2015 and Group 2017 were also analysed for possible confounders, where appropriate, and these confounders were excluded for a re-analysis.

Results: There were 52 patients in Group 2015 and 60 patients in Group 2017. No difference was found in the duration of ICU length of stay (LOS) (median 5 vs 8.5 days, $p = 0.1$) or mechanical ventilation (median 91 vs 129 hours, $p = 0.44$) between the 2 groups. Those who were sedated with dexmedetomidine had better initial prognoses (median APACHE II 13 vs 18), were sedated for greater fractions of their total ICU admission times (median 46% vs 25%) and had a higher incidence of hypotension and bradycardia (36.7% vs 11.4%, $p < 0.01$); which did not relate to a higher mortality. Spearman rank correlation coefficients also showed a weak to moderate association with longer ICU stay and ventilation duration when the duration of sedation with midazolam or propofol was shorter.

Conclusion: This study did not show a reduction in ICU LOS or mechanical ventilation with the advent of dexmedetomidine in our unit. The absence of regular documentation of sedation levels and scheduled sedation breaks may have contributed to these results. Dexmedetomidine has a role to play in the ICU setting, but it should only be used when clearly indicated, with a clear protocol for its use, in order to warrant its higher cost. Vigilance for hypotension and bradycardia is required when using dexmedetomidine.

Background

1.1 The purpose of sedation in the intensive care unit

The most frequent recollection of a patient's Intensive Care Unit (ICU) stay is pain and this is often associated with the accidental removal or disconnection of vital equipment and infusion lines during periods of agitation caused by pain or discomfort.[1,2]

At follow-up interview, many patients report delusional recollections; when they cannot remember specific facts of their ICU stay, with nightmares and feelings of loss of control often being their only recollection of their ICU admission.[3] Patients in pain and discomfort may be agitated, and ameliorating these precipitants could be all that is needed to calm a patient instead of applying pharmacological or mechanical restraints.[3]

Sedation in the ICU is commonplace (table I). A principal aim of sedation is to render a patient co-operative or unaware in an artificial environment which is possibly very stimulating to the patient and which can lead to agitation and delirium - the latter being associated with worse morbidity and mortality (in up to 27% of mechanically ventilated patients).[4,5]

Table I – Indications for sedation in ICU [1]

- Physiological difficulty in ventilation
- Difficulty in oxygenation
- Ventilator dyssynchrony (mechanical difficulty in ventilation)
- Neuroprotection
- Severe pain (e.g. lactrodectism, polytrauma or dressing changes in burns)
- Refractory status epilepticus
- Severe neuromuscular diseases (e.g.Guillain-Barre)
- Agitation or when a patient becomes a danger to him or herself as a result of agitation

1.2 Sedation practices in the intensive care unit

The term sedation is often interpreted to mean anything from anxiolysis to deep procedural sedation (where patients do not move during deeply painful stimuli).[6] As a result, it is important that the desired level of sedation be clearly defined and regular, scheduled sedation breaks be provided.[1,7–9] Many sedation scales have been developed to this end. Probably the most widely used scale is the Richmond Agitation Sedation Scale (RASS), with the sedation goal being a score of +1 to -2.[3] Other more physiologically based targets have been proposed to monitor sedation in the ICU, such as the use of processed electroencephalography (EEG) monitors.[3,10] It is important to note that sedation may be harmful when used inappropriately and may, contrary to the healthcare provider's intention, lead to longer ICU stay and mechanical ventilation.

Sedation is not always necessary and ancillary methods at addressing the cause of agitation are often effective in patients where deep sedation is not a requirement. Ensuring that a patient is receiving adequate nutrition and hydration contributes significantly towards avoiding unnecessary sedation.[7] The Society for Critical Care Medicine (SCCM) has released

the ABCDEF bundle for the assessment, prevention and management of sedation and delirium in the ICU.[11] The ABCDEF bundle encompasses the early treatment of pain, spontaneous awakening and breathing trials, targeting of sedation, detection and treatment of delirium, exercise and family engagement. One has to remember that sedation does not ensure that a patient is pain-free, and analgesia is probably more important than sedation alone in the critical care setting.[12]

1.3 Commonly used sedatives in the intensive care unit

The choice of sedative (table II) may often not be as important as the dosage used, and the lightest level of sedation that is possible and practicable should generally be targeted, if necessary. Many trials have been conducted to try to prove the superiority of one sedative over another and none has yet met this expectation.[1]

Table II – Sedatives often used in ICU [13]

Hypnotics – Ketamine, Propofol, Thiopentone
Benzodiazepines – Midazolam
Tranquilisers – Haloperidol
Opioids – Morphine, Fentanyl
Alpha 2 agonists – dexmedetomidine, clonidine

Most sedatives are also very highly protein-bound and are excreted by the kidneys, thus the interaction between the pharmacokinetics and the pharmacodynamics of a drug should always be borne in mind in critically ill patients with labile biochemistry.[14]

Despite a condemnation of the use of benzodiazepines for sedation in ICU[3], their relative haemodynamic stability when compared to propofol, and the significantly lower cost of these drugs as compared to dexmedetomidine, give them an advantage in resource-constrained environments.

After the registration of 2,6-diisopropylphenol (propofol) in Europe in 1986, this drug quickly gained popularity as a general anaesthetic and sedative, due to its titratability and wide range of effects.[16] It is important to note that, as with any drug, propofol is not without its risks, eg hypotension and metabolic acidosis from prolonged use.

Classically haloperidol (a typical antipsychotic) has also been used in agitated delirium, to settle patients who appear to be a danger to themselves.

Dexmedetomidine is often used either as a primary sedative, or when others have failed in ICU due to the favourable co-operative sedation profile it provides.[3,14, 15, 17]

1.4 Motivation for and potential implications of studying sedation practice at Universitas Academic Hospital's (UAH) ICU

Between 2015 and 2017 there was a 903% increase in the issuing of dexmedetomidine by the pharmacy at the UAH in Bloemfontein, which was largely attributed to its use in the multidisciplinary ICU. During this time period, the number of ICU beds and staff remained constant, therefore indicating there was an increased preference by ICU physicians for the use of dexmedetomidine during this time period, with the associated increase in cost of sedation related to its use.[18] However, the absolute increase in cost, from this increased use of dexmedetomidine, may have been insignificant if this could have been offset by the saving of even one day's admission to the ICU, as shown in table III.

Table III – Cost implications of sedatives vs one day in ICU [18,19]

- One ampoule of midazolam 5 mg / 3 ml – R3.69
- One vial of propofol 500 mg / 50ml – R46.15
- One vial of dexmedetomidine 200 μg / 2 ml – R440.33
- One day's stay in ICU (consumables not included) – R10 158

1.5 Aim of the study

The aim of this study was to evaluate whether the introduction of dexmedetomidine resulted in a shorter duration of mechanical ventilation or ICU stay to warrant the increase in cost related to its use.

1.6 Objectives of the study

The objectives of this study were to attempt to identify the potentially resource-sparing benefits of using dexmedetomidine in group 2017 (in comparison to midazolam and / or propofol in group 2015) by looking at the following parameters:

Primary outcomes

- Duration of mechanical ventilation
- ICU length of stay (LOS)

Secondary outcomes

- Adverse events during sedation: (as are identifiable during a retrospective document review)
    - Hypotensive incidents
    - Incidents of bradycardia
- Influence of APACHE II score on primary outcome
- Average sedation times (also as compared to ventilation periods and duration of ICU stay)
- Serum creatinine and
- Serum albumin (to see if they were significantly different)
- Outcome (death or discharge)

Methods

This study was designed as a retrospective cohort analysis. Institutional Ethics (UFS-HSD2018/0542/2808) and Free State Department of Health approval was obtained. Funding was obtained from the Research Committee of the Three Schools of Medicine, UFS to secure a research assistant who helped with collecting file numbers and files. Drug dispensing registers in the multidisciplinary ICU were used to identify patients who were recorded to have received propofol or midazolam in 2015, as well as patients who were recorded to have received dexmedetomidine in 2017 (convenience sampling). These patients' medical records were collected from the Department of Critical Care at the Universitas Academic Hospital, Bloemfontein, and their files were searched for: age, sex, weight, prescriptions, daily treatment and fluid balance charts, doctors' notes, admission and discharge summary information (including admission and final diagnoses), APACHE II score, creatinine and albumin tests, and heart rate and blood pressure data.

Inclusion criteria

- All patients 18 years and older.
- All patients admitted to the Multidisciplinary ICU from 1 January 2015 to 31 December 2015 and from 1 January 2017 to 31 December 2017.
- All patients that were sedated in the Multidisciplinary ICU (either with dexmedetomidine in 2017, or with propofol / midazolam in 2015).

Exclusion criteria

- Incomplete or lost files (patients had to be identifiable, have prescription and flow charts indicating the sedative, dose, entire duration of sedation and duration of ventilation with complete vitals data for the period of sedation)

The fact that the introduction of dexmedetomidine during 2016 was not protocolised may have led to a preference in its selection as a sedative drug by some intensivists. This point was introduced during the planning phase of this study and it was decided, for the sake of trying to achieve homogeneity in the two cohorts, to compare the sedative practices of 2015 with those in whom dexmedetomidine was used in 2017.

This information was entered into an individual data sheet per patient. Calculations were then made to determine the following: total doses of sedatives given during admission, doses of sedatives given per kilogram per hour (maximum and minimum ranges), total hours of sedation and mechanical ventilation, sedation time per hour of admission and sedation time per hour of ventilation. Figure 1 shows how many files were included for analysis.

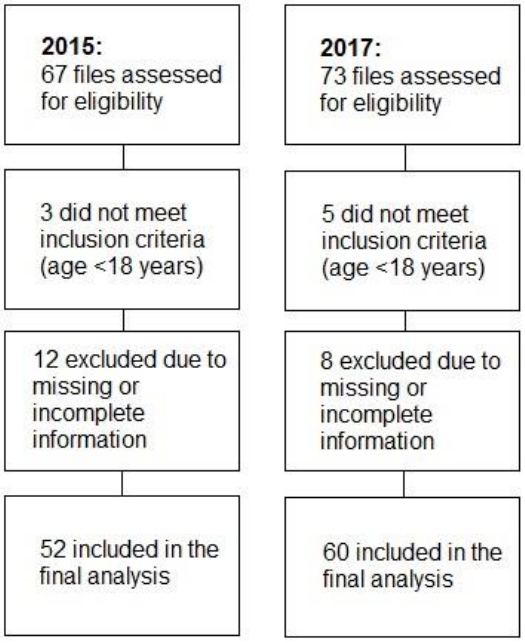

Figure 1 – Files found and excluded from analysis

Patients' diagnoses were then classified into the following pathological categories (a patient was classified into multiple categories, if appropriate): sepsis, trauma, postoperative, oncology, obstetric, neurosurgical, urology, vascular, general surgery, pulmonology, neurology, cardiology, poisoning, haematology, ENT, plastic surgery, cardiothoracic, rheumatology. After an initial pilot study with four data sheets, it was decided to rather identify any incidences of hypotension and bradycardia as single events than to gather complete information regarding heart rate and blood pressure ranges and means. The reason for this was that the process to analyse hypotension and bradycardia throughout (retrospectively) could not be representative of the effects of the sedatives only, the data was only recorded hourly (thus significant periods of hypotension or bradycardia could have been missed) and that there were too many confounders that could have affected single readings. The institutional definitions for hypotension were a systolic blood pressure of less than 90mmHg or a mean pressure of less than 65mmHg; while the institutional definition for bradycardia was any heart rate less than 60 beats per minute.

The gathered data was then entered into a single summary sheet for analysis. Analysis was done with the SAS version 9.4 software. All numerical data was found to have skew distributions and were therefore summarised by range, interquartile ranges and medians. Categorical variables were summarised by frequencies and percentages. The statistical comparison of the two year groups were done using Mann-Whitney tests (numerical variables) and chi-squared or Fisher's exact tests (categorical variables). 95% confidence intervals (CIs) were calculated for main outcome differences.

Spearman rank correlation tests were calculated to ascertain whether sedation time (converted to days), when calculated as a fraction of either ICU LOS (days) or mechanical ventilation time (converted to days), influenced the primary outcomes.

Results

The demographic data (table IV) indicate that during their periods of sedation in ICU, the cohorts were similar, except for the interquartile range of estimated weight (95% CI for median difference 2015-2017 -10, 0), APACHE II score (95% CI for median difference 2015-2017 1;8) and the lower limits of albumin levels (with lower troughs being found in the 2017 cohort, 95% CI for median difference 2015-2017 0;5).

Table IV – Demographics and laboratory values (* = p value ≤ 0.05)

	Median 2015 (interquartile range)	Median 2017 (interquartile range)	p-value
Age (years)	40 (26 – 54.5)	32.5 (26.5 – 51)	0.50
Weight (kg)	70 (60 – 75)	70 (65 – 80)	0.04*
APACHE II	18 (14.5 – 24)	13 (8 – 21)	0.01*
Creatinine lower (µmol/L)	57 (43 – 117.5)	48 (35 – 92)	0.25
Creatinine upper (µmol/L)	103 (73 – 216)	106.5 (72.5 – 213)	0.73
Albumin lower (g/L)	16 (12.5 – 21.5)	14 (11 – 17.5)	0.05*
Albumin upper (g/L)	22 (16 – 28)	23 (19.5 – 27)	0.65
Sex	N (%)	N (%)	
Male	29 (55.8)	27 (45.0)	0.26
Female	23 (44.2)	33 (55.0)	

When examining primary outcomes, it is apparent that the cohorts did not significantly differ in the total duration of ICU LOS (95% CI for median difference 2015-2017 -4; 0) or mechanical ventilation (95% CI for median difference 2015-2017 -54;24, see figures 2 and 3), although the 2017 cohort did receive sedation for significantly longer, 95% CI for median difference 2015-2017 -72;-20 (table V).

Table V – Primary outcomes and sedation times († = p value ≤ 0.01)

	Median 2015 (interquartile range)	Median 2017 (interquartile range)	p-value
ICU stay (days)	5 (2 – 14)	8.50 (5 – 12.50)	0.10
Sedation time (hours)	33.5 (15 – 68)	87 (33.5 – 162)	0.01 †
Ventilation duration (hours)	91 (34 – 272)	129 (58 – 221)	0.44
Sedation per days admitted (fraction)	0.25 (0.13 – 0.53)	0.46 (0.26 – 0.72)	<0.01 †

Sedation per ventilation time (fraction)	0.43 (0.18 – 0.82)	0.94 (0.58 – 1.00)	<0.01 †

Analysis of pathological categories showed no statistically significant difference between Group 2015 and Group 2017. However, there was a trend towards more patients for postoperative stays being admitted in 2015 (11 (21.2%) vs 5 (8.3%), p = 0.05) and more patients with neurological diagnoses being admitted in 2017 (10 (16.7%) vs 3 (5.8%), p = 0.07). In order to remove the influence of these two pathological categories on the results, the data was therefore re-analysed, with these patients excluded from the cohorts (postoperative admissions tend to have shorter ICU LOS, and patients with neurological diagnoses, such as Guillain-Barre disease, tend to have longer and more complicated ICU admissions).

This re-analysis demonstrated that after excluding the influence of these pathological categories, the duration of ICU stay was significantly longer in Group 2017 compared to Group 2015 (median ICU LOS nine days in 2017 vs five days in 2015, p = 0.04). However, duration of ventilation remained similar (p = 0.35). The fractions of time that patients were sedated for, as compared to their ICU stay and duration of mechanical ventilation were also significantly higher in 2017.

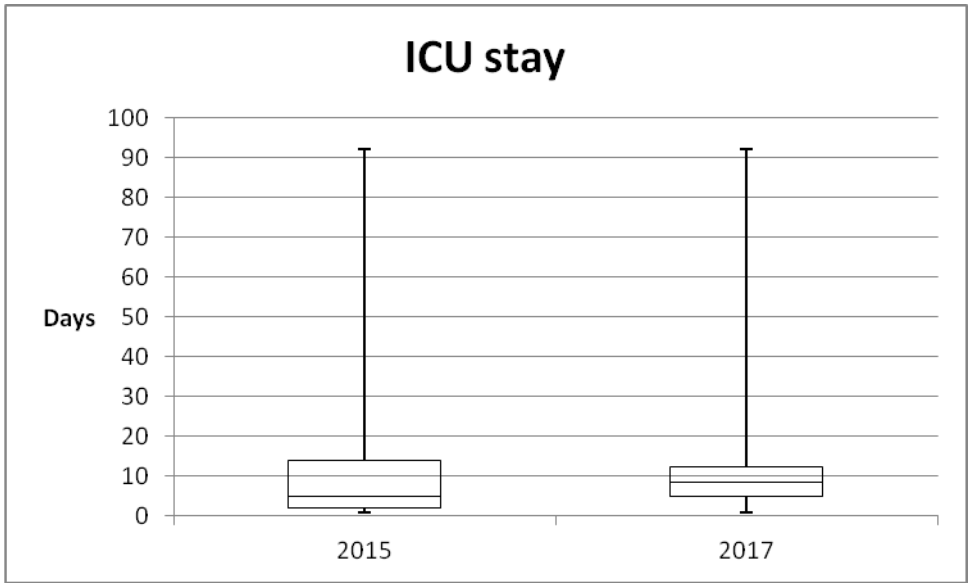

Figure 2 – A comparison of length of ICU stay between groups 2015 and 2017

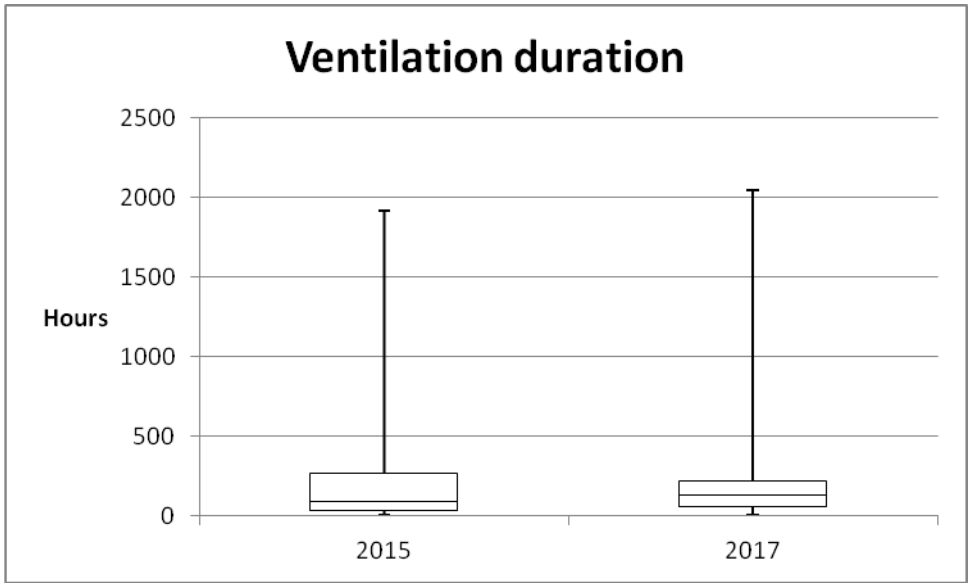

Figure 3 – A comparison of duration of ventilation between groups 2015 and 2017

Spearman rank correlation coefficients for 2015 were negative when the fraction of sedation per days admitted was compared to ICU LOS (-0.48, p = <0.01), and the sedation per days ventilated was compared to duration of mechanical ventilation (-0.51, p = <0.01). The same was not found with the use of dexmedetomidine in 2017.

Patients who were discharged alive in 2017 (and sedated with dexmedetomidine) were sedated for significantly longer periods of their ventilation time, as compared to those who were sedated with propofol or midazolam in 2015 (n = 36 (60.0%) (2017) vs n = 32 (61.5%) (2015), sedation per ventilation time median 2017 = 0.99 vs 2015 = 0.29, p = 0.02).

Patients who were sedated with dexmedetomidine in 2017 had a higher incidence of cardiovascular side effects (43.3% vs 11.5%, p < 0.01), which included both bradycardia and hypotension, as compared to Group 2015.

When patients were stratified according to APACHE II scores (0 – 19, 20 – 29 and >30) there was a trend towards longer ICU stay in 2017 in the cohort with APACHE II scores 0 - 19 (median ICU stay 8.5 vs 5, p = 0.07), however duration of mechanical ventilation was not affected (table VI). The patients' mortality rates in this study were within the limits of acceptability as predicted by their APACHE II scores, and did not differ between the cohorts (table VI).(20)

Table VI – Mortality per APACHE II strata

APACHE II:	Mortality 2015 n (%)	Mortality 2017 n (%)	p-value
0 – 19	7 (25.9)	10 (23.8)	0.84
20 – 29	6 (40)	6 (50)	0.60
>30	4 (66.7)	3 (75)	1.00

Discussion

This study did not find that there was a reduction in duration of ICU stay or mechanical ventilation following the introduction of dexmedetomidine for sedation in the Multidisciplinary ICU. The current body of evidence supports the finding, except when agitated delirium has been diagnosed or when co-operative sedation is required for other reasons.[21]

The results also showed that patients who were sedated on ICU with dexmedetomidine in 2017 tended to have better prognoses than those who were sedated with propofol or midazolam in 2015, but, nevertheless, were sedated for longer. When those with diagnoses that could have confounded these findings (patients who were admitted for postoperative observation or with neurological conditions necessitating ICU admission) were excluded, this uncovered an association with longer ICU stay in the dexmedetomidine group.

The use of dexmedetomidine (especially at higher ratios to duration of admission or ventilation – likely due to the more favourable sedation profile clinically) was associated with a higher incidence of side effects. This practice did not seem to affect mortality. This finding is in keeping with Mirski *et al*, who showed that the use of dexmedetomidine was associated with more incidents of bradycardia.[22] This reinforces the point that the choice of sedative for the individual patient, and how it is used, are likely more important to the outcomes of the patient than habitual preference of one drug over another.[23] The finding that patients who were discharged alive in Group 2017 with higher ratios of sedation per ventilation time is also opposed to current literature.[24]

Reade *et al* showed a 17.3 hour improvement in mean ventilator-free time at 7 days when dexmedetomidine was used in agitated delirium.[21] Due to this evidence base, it was postulated that dexmedetomidine would perform superiorly when compared head-to-head with other sedatives in a randomised controlled trial, but the SPICE III trial did not substantiate this belief.[24] Dexmedetomidine has been shown to have benefits over midazolam with regards to mechanical ventilation, but at the risk of added cardiovascular side effects.[21,25]

Propofol is a potent vasodilator with negative inotropic and chronotropic effects. It is also associated with propofol-related infusion syndrome.[3,14] Dexmedetomidine has also been shown to be non-inferior to propofol with regards to the incidence of delirium, duration of mechanical ventilation and length of ICU stay.[25,26]

The Intensive Care Society recommends non-benzodiazepine strategies over benzodiazepine strategies, but this recommendation has not permeated to all units.[3] Two randomised controlled trials showed that midazolam was associated with both a higher incidence and longer duration of delirium when compared to dexmedetomidine.[25–27] Zaal et al showed in 2015 that the deliriogenic effects of midazolam are dose-dependent and are more prevalent with continuous infusions.[28] Lorazepam has not escaped this scrutiny, with the MENDS study showing that dexmedetomidine use was associated with more delirium-free and coma-free days in ICU.[29] When compared to midazolam, propofol has been shown to reach sedation targets earlier with faster recovery after cessation of the infusions.[30]

A recent randomised controlled trial has not showed that the use of typical or atypical antipsychotics are superior to placebo in reducing the duration of either hyperactive or hypoactive delirium. The use of benzodiazepines is not supported by recent guidelines in sedation or the management of delirium.[10,31]

Early deep sedation has been shown to result in longer times to extubation and higher 180 day mortality rates.[15] One randomised controlled trial showed that lighter levels of sedation were associated with shorter ICU stay and duration of mechanical ventilation versus deeper sedation.[32]

Although there was no statistically significant difference in the primary outcomes between prognostic strata, a trend to longer ICU stay and the use of dexmedetomidine in the APACHE II 0 - 19 group is counterintuitive to what most critical care practitioners would hope to achieve for seemingly healthier individuals.

Strøm et al first described the benefits of analgosedation in 2010. They showed that the use of morphine alone (as compared to morphine and sedation) reduced ventilated days, and this reinforced the stance that effective analgesia alone may obviate the need for pure sedatives.[12] This study supported the use of analgesia in ICU (and forms part of the rationale behind the motivation for adequate analgesia in the current guidelines). The analgesic properties of dexmedetomidine, and the association with lower opioid requirements when it is used, may also have led to the belief that it would perform superiorly according to the principles of analgosedation.[14]

The ABCDEF bundle has been validated by Pun et al, in over 15 000 patients, to reduce the incidence of death within the first 7 days, next-day mechanical ventilation, coma, delirium, physical restraint use, ICU readmission, and discharge to a facility other than home; thus this bundle should receive strong consideration for implementation in units such as ours.[33]

The negative Spearman Rank Correlation Coefficients (sedation per days admitted compared to ICU LOS and sedation per days admitted compared to duration of ventilation) in 2015, indicate a weak to moderate association with longer ICU LOS and ventilation hours. This association was when less sedation was given with propofol and / or midazolam per period of time in ICU. This finding is contrary to current literature indicating that longer sedation times lead to longer ICU stay and increased morbidity.[34]

Limitations

The study design was retrospective in nature and therefore causality is difficult to determine, due to uncontrolled confounders. The sample size was limited and may have affected the determination of statistical significance. Vital signs were only recorded every hour and episodes of hypotension and / or bradycardia may have been missed. As mentioned previously, selection bias may have played a role in the sedation practices in 2017, as propofol and midazolam were in use during that year, although analysis did not show a statistically significant difference in pathological categories. Patients' weights were often estimated by their treating physicians and this may have also influenced calculations regarding the weight-indexed doses of sedatives. Sedation targets were not documented, if

used, and the lack of scheduled sedation breaks may also have influenced the duration of mechanical ventilation, ICU length of stay and final outcomes.[8,9]

The implementation period regarding the use of dexmedetomidine in 2016 may have played a large role in the decision as to which drug to use to sedate any particular patient by a given intensivist during the 2016 – 2017 period. This trend may have continued into 2017, but it is difficult to analyse retrospectively as the decision on which drug to use was neither protocolised in our unit, nor was the reason for the decision on why to use individual sedatives routinely recorded.

The arbitrary limits that were defined for hypotension and bradycardia are controversial, but for the sake of uniformity limits had to be defined.[35]

While the APACHE II score, as a physiologically-based prognostic score, has its limitations and has been largely replaced by newer scores, its simplicity and ease of use make it a regularly utilised tool in our unit.[36]

Conclusion

This study did not show a reduction in ICU LOS or mechanical ventilation with the advent of dexmedetomidine in our unit. This study showed a significant association with longer time of sedation with the use of dexmedetomidine in 2017 as compared to propofol and / or midazolam in 2015. This finding was contrary to the belief that introducing the use of dexmedetomidine more regularly in our unit would lead to shorter ICU LOS and mechanical ventilation. There was also a significantly higher incidence of side effects with the use of dexmedetomidine, although mortality was unaffected. It should be noted that dexmedetomidine has a definite place in the management of the critically ill patient. Sedation in the ICU (with any drug) should be 1) indicated, 2) targeted and 3) withdrawn or interrupted, where appropriate As a result, it is a recommendation of this study that sedation be practiced as outlined in the Society of Critical Care Medicine's Clinical Practice Guideline for the Prevention and Management of Pain, Agitation and Delirium.[10]

The findings of this study, in the face of its appreciable limitations and retrospective nature, should by no means serve to remove the use of dexmedetomidine in the critical care unit. These findings should serve as a warning against the indiscriminate use of dexmedetomidine sedation in ICU.[3,10] In developing countries, where resources are sparse, newer and more expensive drugs should be used as alternatives to cheaper sedative agents only where their higher cost could potentially be offset in other areas. More prospective research is needed in this area in developing countries to determine whether the appropriate use of dexmedetomidine may be linked with such benefits.

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Appendix A

UNIVERSITY OF THE FREE STATE
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YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

03-Aug-2018

Dear **Dr Reinier Swart**

Ethics Clearance: **The possible association of shorter mechanical ventilation and / or ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2015 versus 2017.**

Principal Investigator: **Dr Reinier Swart**

Department: **Anaesthesiology (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2018/0542/2808**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784

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Health Sciences Research Ethics Committee

28-Nov-2018

Dear **Dr Reinier Swart**

Ethics Number: UFS-HSD2018/0542/2808

Ethics Clearance: **The possible association of shorter mechanical ventilation and / or ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2015 versus 2017.**

Principal Investigator: **Dr Reinier Swart**

Department: **Anaesthesiology Department (Bloemfontein Campus)**

SUBSEQUENT SUBMISSION APPROVED

With reference to your recent submission for ethical clearance from the Health Sciences Research Ethics Committee. I am pleased to inform you on behalf of the HSREC that you have been granted ethical clearance for your request as stipulated below:

- Amendments made to the data sheets and protocol

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this request for ethical clearance and we wish you continued success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
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Appendix B

health
Department of Health
FREE STATE PROVINCE

26 July 2018

Dr R Swart
Dept. of Anaesthesiology
UFS

Dear Dr R Swart

Subject: The possible association of shorter mechanical ventilation and / or ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2015 versus 2017.

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** lithekom@fshealth.gov.za or sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 27/07/18

Appendix C

UNIVERSITY OF THE FREE STATE
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[redacted]

12 June 2018

Chairperson
Ethics Committee
Health Sciences Faculty

RE : DR R SWART

Study Title

The possible association of shorter mechanical ventilation and / or ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2015 versus 2017.

This is to certify that I am aware of Dr R Swart's project and approve it.

He is requesting approval from the Ethics Committee to commence with data collection and to proceed with the research.

Yours sincerely,

DR. N.E. PEARCE
University of the Free State
Academic Hospital Complex
12-06-2018
Head of Department: Surgery

DR N.E. PEARCE
HEAD: DEPARTMENT OF SURGERY AND CRITICAL CARE
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UNIVERSITY OF THE FREE STATE
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Date: 11th June 2018

Dr E Le Grange
Chairperson: Ethics Committee
FACULTY OF HEALTH SCIENCES

Re: Permission to conduct study

I hereby grant permission for the following study to be performed as part of the MMed Study of Dr Reinier Swart.

TITLE: **The possible association of shorter mechanical ventilation and / or ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2015 versus 2017.**

Regards,

Gillian Lamacraft (Prof)
Acting HOD
Department of Anaesthesia

KONSULTANTE/CONSULTANTS: Prof(s) Diedericks, G Lamacraft, CL Odendaal, AM Kachelhoffer; Drs MA Pearson, MG Selebaki, Lemmer, NP Wessels, A Theron, N van der Westhuizen, R Nsaba
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Date: 10 June 2018

Dr E Le Grange
Chairperson: Ethics Committee
FACULTY OF HEALTH SCIENCES

I hereby grant permission for the following study to be performed as part of his MMed Study:

Re: Permission to conduct study

Hereby a request for the following study to be performed:

TITLE: **The possible association of shorter mechanical ventilation and / or ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2015 versus 2017.**

The Principal Investigator is:

Dr Reinier Swart

.....

DR SD MAASDORP
HEAD OF CLINICAL UNIT: DEPT. CRITICAL CARE

Dr. SD Maasdorp, HEAD OF CLINICAL UNIT: DEPT. CRITICAL CARE 339 (G60), Bloemfontein 9300, South Africa/Suid-Afrika
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Appendix D

PROTOCOL

Dr. R. Swart, - M. B. Ch. B. (Pret.), D.A. (SA)
Registrar in the Department of Anaesthesiology
University of the Free State

TITLE

The possible association of shorter mechanical ventilation and / or ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2015 versus 2017.

RESEARCHERS

Researcher:	R. Swart
Study Leader:	Dr S. Maasdorp (Department Critical care)
Co-supervisor:	Prof. G Lamacraft (Department Anaesthesiology)
Data collectors:	R. Swart, Sr G Joubert (research assistant)
Biostatistician:	Prof. G Joubert

INTRODUCTION

Sedation in the critical care unit is a very commonplace practice. The most frequent recollection of a patient's ICU stay is pain(1) and this "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International association for the study of pain definition of "pain")(2) is often associated with the accidental removal or disconnection of vital equipment and lines.

One has to remember that sedation does not mean a patient is pain-free, and analgesia is equally important in the critical care setting. The principal aim of sedation is often to render a patient co-operative or unaware in an artificial environment which is possibly very stimulating to the patient (the intensive care unit) and which can lead to agitation, delirium - which are associated with worse morbidity and mortality (in up to 27% of mechanically ventilated patients).(3,4) Thanks to newer ventilators and ventilator modes, ventilator dyssynchrony is a less common occurrence, but sedation is often required for other reasons (see table I).(1)

Table I – Indications for sedation in ICU(1)

- Difficulty in ventilation
- Ventilator dysynchrony
- Neuroprotection for raised intracranial pressure
- Difficulty in oxygenation
- Increased work of breathing
- Severe pain (e.g. lactrodectism, polytrauma or dressing changes)
- Refractory status epilepticus
- Severe neuromuscular diseases (e.g.Guillain-Barre)

Sedation is not always necessary and ancillary methods at anxiolysis are often effective in patients where deep sedation is not a requirement. In fact, seeing to a patient's daily feeding and hydration requirements may go a long way towards avoiding unnecessary sedation.(5) Deep and unnecessary sedation is also associated with worse morbidity and mortality and prolonged mechanical ventilation in ICU. It is therefore a requirement to assess the level of a patient's sedation frequently and provide regular, scheduled sedation breaks (which are also associated with lower total sedative dosages).(1,5)

The choice of sedative may often be as important as the dosage used and the lightest level of sedation that is possible and practicable should generally be targeted. One randomised controlled trial showed that lighter levels of sedation were associated with shorter ICU stay and duration of mechanical ventilation versus deeper sedation.(6) Many trials have been conducted to try to prove the superiority of one sedative over another and none has yet proven to be superior in large, randomised studies.(1) A few examples of commonly used sedatives are presented in table II.

Table II – Sedatives often used in ICU(7)

Hypnotics – Ketamine, Propofol, Thiopentone
Benzodiazepines – Midazolam
Tranquilisers – Haloperidol
Opioids – Morphine, Fentanyl
Alpha 2 agonists – dexmedetomidine

Table III – Properties of the ideal sedative(7)

- Pharmaceutics
  - Ease of administration
  - Does not promote growth of pathogens
  - Easily prepared and long shelf life

  Pharmacodynamics
  - Predictable dose-dependent effects with minimal individual variation
  - Provides appropriate sedation, anxiolysis, amnesia and analgesia
  - No tolerance and withdrawal symptoms
  - Provides facilitation of ventilator synchrony and the performance of various procedures and nursing interventions

  Pharmacokinetics
  - Rapid onset of action
  - Easily titratable level of adequate sedation
  - Short-acting, allowing patient assessment, rapid recovery following discontinuation, easy weaning from mechanical ventilation, and early extubation
  - Minimal metabolism; not dependent on normal hepatic, renal, or pulmonary function
  - No active or toxic metabolites
  - Safe for all ages with no age-related changes in pharmacokinetics
  - Lack of accumulation with prolonged administration

  Interactions

- No or minimal interactions with other drugs

No or few adverse effects

- No anaphylaxis or allergic reaction
- No nausea, vomiting, or phlebitis
- Minimal respiratory depression
- Minimal effect on cardiovascular function
- No pain on injection
- No suppression of cortisol production by the adrenal cortex

Other

- Cost effective
- Lack of abuse potential
- Widely available

Dexmedetomidine is often used either as a primary sedative, or when others have failed in ICU due to the theory that it causes co-operative sedation.(8) This has led to several small studies which have tried to investigate the possible superiority of dexmedetomidine over other conventional ICU sedatives, but the literature is currently inconclusive. Dexmedetomidine seems to have benefits over Midazolam with regards to mechanical ventilation, but at the risk of added side effects - for example cardiovascular instability in a population that is vulnerable to haemodynamic compromise.(9)

The pharmacological properties of dexemedetomidine (as an ICU sedative) are listed in the table below (as well as dosing guidelines and contraindications):(8)

Table IV – Pharmacokinetics of Dexmedetomidine

Dose:	Loading: 1mcg/kg ivi over 10 – 30 minutes Maintenance: 0.2 – 0.7 mcg/kg/hour
Contraindications:	- Compromised critically ill patients - Heart block Caution in: - Concomitant neuraxial anaesthesia
Adverse effects:	- Prolonged infusions may lead to drug accumulation, emergence delirium, dependence and withdrawal phenomena. - Adrenal steroid production may be inhibited. - Inhibition of insulin secretion. - Initial hypertension (especially with a loading dose), followed by hypotension and bradycardia. - Nausea and dry mouth. - May potentiate respiratory depression of other analgesics and sedatives.
Pharmacodynamics:	Alpha2-adrenergic agonist – meaning it causes presynaptic auto-inhibition of the autonomic nervous system. Different types of alpha 2 receptors are located throughout the body allowing for analgesia, central sympatholysis, neuroprotection and altered cognition.
Pharmacokinetics:	Dexemedetomidine is primarily administered as an IV infusion during ICU sedation. Its onset of action is 15

	minutes. Its beta half-life is around 2 hours, meaning that it would take approximately 8 to 10 hours to achieve steady state (and this is why a loading dose is essential, but could be detrimental to the critically ill patient if their physiology is too unstable). Context-sensitive half-time is estimated at 20 – 30 minutes. The drug is also 94% protein-bound to albumin and alpha1-acid glycoprotein (so downward dosage adjustments are required in patients with low albumin levels). It is extensively metabolised in the liver y the cytochrome p450 enzyme system (quadrupling beta half-life in liver failure, and therefore requiring a decrease in maintenance dose; it also has several drug interactions with other drugs metabolised by this system, and may potentiate the effects of other concomitantly administered sedatives) and then 95% excreted in the kidney (and therefore requiring a decreased loading dose).

It is evident from the above table that dexmedetomidine is not a cardiovascularly inert drug and this strengthens the point that the choice of sedative and how it is used is likely more important to the outcomes of the patient than blind superiority of one drug over another.

Below are tables detailing the pharmacological properties of midazolam and propofol as ICU sedatives – the other two drugs commonly used in the multidisciplinary ICU at Universitas Academic Hospital for the purposes of sedation:(8)

Table V – Pharmacokinetics of Midazolam

Dose:	0.25 – 1mcg/kg/min
Contraindications:	Caution in: - The elderly - Co-administration of other sedatives or opioids as cardiovascular stability may be lost
Adverse effects:	- Respiratory depression - Paradoxical agitation at low dosages - Due to amnestic effects, some patients may have dysphoric recollection of the sedation period - May cause cardiovascular suppression when administered with other sedatives or opioids
Pharmacodynamics:	$GABA_A$-agonist – potentiates the binding of GABA toits receptor site and thereby increasing chloride influx and neuronal membrane hyperpolarisation.
Pharmacokinetics:	- Peak effect 2 – 3 minutes (IV) - 96 – 99% plasma protein binding - Extensively metabolised in the liver by CYP3A4 and CYP3A5 - Phase I metabolites are active and are excreted by the kidneys (thus they may accumulate in renal failure)

	- High interindividual variability in metabolism (thus unpredictable pharmacokinetics) - Context-sensitive half-time of 3-15 hours (residual sedation may be effective during sedation breaks, thus worsening outcomes)

Table VI – Pharmacokinetics of Propofol

Dose:	25 – 75 mcg/kg/min
Contraindications:	- Hypovolaemia - Hypotension - Cardiac compromise Caution in: - High doses (>5ml/kg/hour) - Critically ill with energy depletion - Critically ill children - Severe head injury
Adverse effects:	- Hypotension - Myocardial depression - Emulsion emboli - Propofol infusion syndrome - Pancreatitis - Hyperlipidaemia
Pharmacodynamics:	- Prolong the binding of GABA to its receptor - Blocks central nicotinergic receptors
Pharmacokinetics:	- Onset of action 30 seconds - Time to peak effect after a bolus is 90 – 100 seconds - Alpha half-life is 2 – 4 minutes and beta half-life is 30 – 60 minutes - Final elimination is 4 - 23hours (due to its highlyfat-soluble nature) - Context sensitive half-time of less than 40minutes after 8hours - Highly protein-bound (99%)

Since 2015 there has been a 903% increase in the pharmacy issuing of dexmedetomidine at the Universitas Academic Hospital in Bloemfontein (largely attributed to its use in the multidisciplinary ICU). There has not been a proportionate expansion of treatment capacity, indicating an increased preference for the use of dexmedetomidine despite the absence of literature indicating its superiority in most circumstances and despite its greater cost to the hospital.(10) This practice will then have to be offset by other potential benefits and this study aims to identify the possible association with shorter mechanical ventilation and / or ICU stay which may warrant the use of dexmedetomidine as a preffered agent in this setting. The reason these two years are being contrasted to one another is the fact that dexmedetomidine was gradually introduced into practice in this unit during 2016. Therefore, individual consultants slowly began using the drug and 2016 was excluded to prevent the selection bias that may have occurred due to this gradual change in practice from affecting the results.

AIM

The aim of the study is to determine if there is an association with shorter duration of mechanical ventilation and / or length of ICU stay in patients admitted to the multidisciplinary intensive care unit at Universitas Academic Hospital from 1 January 2015 to 31 December 2015 versus those admitted from 1 January 2017 – 31 December 2017 when dexemedetomidine has been used as a single or adjuvant sedative in the critically ill.

Primary outcomes:

- Duration of mechanical ventilation
- Length of ICU stay

Secondary outcomes:

- Adverse events during sedation: (as are identifiable during a retrospective document review)
    - Hypotensive incidents
- Influence of APACHE II score on primary outcome
- Dose per weight
- Average sedation breaks
- Mean creatinine
- Mean albumin
- Outcome (death or discharge)

METHODOLOGY

This study design will be a retrospective document review.

SAMPLE

All adult patients who were admitted and also sedated in the multidisciplinary intensive care unit at Universitas Academic Hospital over the period from 1 January 2015 to 31 December 2015 and 1 January 2017 – 31 December 2017 are to be included in this study. Two cohorts will thus be created to compare to each other.

<u>Inclusion criteria</u>

- ❖ All patients 18 years and older.
- ❖ All patients admitted to the multidisciplinary intensive care unit over 1 January 2015 – 31 December 2015 and 1 January 2017 – 31 December 2017.
- ❖ All patients that were sedated (either with dexemedetomidine, propofol or any benzodiazepine).

<u>Exclusion criteria</u>

- ❖ Incomplete or lost files.

Assuming a bed occupancy rate of 85.7% per day (6/7 beds) with an average ICU length of stay of 7 days – with approximately 4 /6 patients requiring sedation, the total sample size is estimated at 416 patients.

MEASUREMENT

The medical records of all patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital will be reviewed for all patients admitted from 1 January 2015 to 31 December 2015 and 1 January 2017 – 31 December 2017. The following information will be collected from these records (on individual data collection sheets):

- Demographic data:
  - Age
  - Gender
  - Length of ICU stay
  - Weight
  - Patient identifier (not to be included in the final reporting of data)
- Clinical data:
  - Primary diagnosis
  - Mechanical ventilation (Yes / No)
    - Duration of mechanical ventilation (hours)
    - Reintubated (Yes / No)
  - Sedation (Yes / No)
    - Duration of sedation (hours)
    - Average sedation breaks
  - Sedative:
    - Drug (s)
    - Dosing range (mcg/kg/min)
    - Total dose
  - Side effects of drugs
  - Hypotensive incidents (as defined by Universitas Multidisciplinary ICU)
  - Indication for sedation
  - Mean albumin during sedation
  - Mean creatinine (or eGFR, if available) during sedation
  - APACHE II score
  - Outcome (death or discharge)

Medical records will be investigated for the following information:

- Times of initiation and completion of sedation
- Times of intubation and extubation
- Infusion rates of drugs
- Haemodynamic data
- Indications for sedation
- Side effects of sedatives

- APACHE II score

Laboratory flow charts will be investigated for biochemical data.
This data will be collected by both the research assistant, as well as the primary investigator.

METHODOLOGICAL AND MEASUREMENT ERRORS

This study is dependent on the accurate and complete reporting of clinical information by the healthcare professionals involved in the care of the critically ill patients. Critically ill patients require frequent and continuous monitoring, therefore this data should be readily and accurately available, but when emergencies in the unit occur the documentation of times may be slightly inaccurate due to delayed reporting. If laboratory data is missing or lacking, this may confound the finding of adverse events.

This study can also only determine if there is an association and causality will have to be determined by a later prospective, randomised controlled trial.

PILOT STUDY

The first 4 cases will be considered the pilot study to assess the applicability of the data collection sheet and completeness of information (although the author has worked in the intensive care unit prior to this study and believes the information should be adequate) and will be included in the final data analysis.

ANALYSIS

The researcher will enter the data into an Excel spread sheet. Statistical analysis will be done by the Department of Biostatistics of the University of the Free State.
Results will be summarised by means and standard deviations or percentages depending on data distributions for continuous variables (e.g. length of mechanical ventilation) and categorical variables will be summarised in terms of median, mode and range. The groups will be compared using a 95 % confidence interval for differences in means, medians or percentages (with appropriate hypothesis testing).

The two cohorts will also be stratified according to APACHE II scores and compared for primary and secondary outcomes to be able to more accurately exclude prognosis from influencing the final analysis. The groups will be stratified into three categories:
APACHE II score 0 – 19 (overall approximate mortality < 30%)
APACHE II score 20 – 29 (overall approximate mortality < 50%)
APACHE II score >30 (overall approximate mortality >50%)

IMPLEMENTATION OF FINDINGS

From this data we will determine whether the recent change in practice to the addition of dexmedetomidine as a primary or adjuvant sedative is associated with a decrease in ICU length of stay and / or mechanical ventilation at the multidisciplinary intensive care unit at the Universitas Academic Hospital (and, by implication, the added cost of the drug). These findings may also lead to the production and implementation of a sedation checklist (Appendix H) and recommendations at the Universitas Academic Hospital's multidisciplinary intensive care unit.

These findings will be presented for publication in the South African Journal of Anaesthesia and Analgesia.

TIME SCHEDULE

After obtaining approval from the ethics committee and relevant authorities data will be collected.

HSREC approval – obtained 3 August 2018 (final approval)
FS DoH approval – obtained 30 July 2018

Data collection will take approximately 2 months (1 December 2018 – 31 January 2019) and analysis in the range of 1 month (February 2019).

BUDGET

A data collection sheet costs 50c to print in monochrome from the Department of Anaesthesiology. If any adverse events are identified that page will be copied and kept as a drug adverse event example in the research database.

Data sheets	-	R0.50 incl. VAT

Estimate of 416 samples

Provision for the possibility of adverse events – 100 samples

Pens (pack of 20 black – Bic)	-	R125 from Takealot.com
Research assistant	-	R 4000
Total cost	-	R 4383 (724x R00.50 + R125 + R4000)

Currently the South African Society of Anaesthesiologists sponsors publications in the South African Journal of Anaesthesia and Analgesia, so no publication fees are being made provision for.
The Department of Anaesthesiology and the University of the Free State provide funding for research up to R10 000 and application will be made to the department and university to cover these costs.

ETHICAL ASPECTS

This is a retrospective analysis of the clinical records of patients that had already been admitted to the multidisciplinary intensive care unit at the Universitas Academic Hospital. While all due care and responsibility will be taken to ensure that no patient identifiers are published or made known outside of the clinical records and the researchers, no other ethical problems are foreseeable in this retrospective document review. Informed consent for treatment was already obtained from patients and / or clinical managers and / or family prior to admission to and treatment in the intensive care unit.

The roles of the research assistant will be as follows:

- Collection of files
- Entry of data into data sheet
- Reporting to primary investigator all data sheets for review
- Assigning unique identifiers to files to mask patient identity in the following format (unique identifiers not to appear in final report): 15/d/0001 (15 – year of admission; d – dexmedetomidine, m – midazolam, p – propofol; 0001 – unique number for patient record)

The research assistant has consented to the above roles and will maintain patient confidentiality by only examining files on hospital premises and by consenting to not sharing any information outside of this study.

If any adverse events regarding patient sedation and / or the use of specific sedatives are identified, they will be reported to the Medicines Control Council and the relevant unit manager.

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Appendix E

Research data sheet: Dexmedetomidine vs sedatives Data sheet number _____ / _____	
Number:	
Identifier:	
Age:	
Gender:	
ICU stay (days):	
Weight:	
Diagnosis:	
Sedative:	
Why sedate?	
Dose range:	
Total dose:	
Sedation time (hours):	
Vent (y/n):	
Vent duration (hours):	
Reintubated (y/n):	
Side effect (y/n):	
Side effect:	
APACHE II	
Creat/eGFR	
Albumin	
Incidents of hypotension	
(sBP <90mmHg, or mBp	
<65mmHg)	
Sedation break	
Outcome	
Vasoactive medications	

Data summary sheet:

Number:	Age:	Gender:	ICU stay (days):	Weight:	Diagnosis:	Category		
						Sepsis	Trauma	Postoperative

				Sedative:	Dose range:			
Oncology	Obstetric	Neurological			Lower	Upper	Lower	Upper

Data summary sheet

Total dose:		**Sedation time (hours):**	**Vent (y/n):**	**Vent duration (hours):**	**Reintubated (y/n):**
Drug 1	Drug 2				

Side effect (y/n):			APACHE II	Creat/eGFR		Albumin	
Side effect 1	Side effect 2	Side effect 3		Lower	Upper	Lower	Upper

Incidents of hypotension	Outcome	Vasoactive medications				Comment
		Med 1	Med 2	Med 3	Med 4	

Appendix F

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- The submitting/corresponding author is duly authorised to herewith assign copyright to the South African Society of Anaesthesiologists (SASA).
- All co-authors have made significant contributions to the manuscript to qualify as co-authors.
- Ethics committee approval has been obtained for original studies and is clearly stated in the methodology.
- A conflict of interest statement has been included where appropriate.
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The following are sample references:

1. Jun BC, Song SW, Park CS, Lee DH, Cho KJ, Cho JH. The analysis of maxillary sinus aeration according to aging process: volume assessment by 3-dimensional reconstruction by high-resolutional CT scanning. Otolaryngol Head Neck Surg. 2005 Mar;132(3):429-34.
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The association of duration of mechanical ventilation and ICU stay with the use of dexmedetomidine as a single or adjuvant sedative versus other sedatives in critically ill patients in the multidisciplinary intensive care unit at the Universitas Academic Hospital in Bloemfontein, 2018 versus 2017.

By

Reinier Swart

Submitted in fulfilment of the requirements for the degree

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in the Department of Anaesthesiology of the

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Appendix H

Daily sedation and delirium checklist and plan	
Patient sticker:	If no sticker is available – Name and surname: File number / Date of birth: / dd/mm/yyyy Total ICU stay (days):
Current sedation plan: (include – sedative, indication and planned stopping date and time)	
Was there a planned sedation break and spontaneous breathing trial? If no, supply reason.	
Is there an acute change / fluctuating course of mental status?	
If so, do CAM-ICU.	Positive / Negative
If positive – orientate patient, provide analgesia, ensure all sensory demands are met (eg hearing aid / reading glasses)	Mental state normalised: Yes / No
Type of delirium	Agitated / Hypoactive
Is sedation indicated? (First consider exercise, family engagement and non-pharmacological treatment)	Yes / No
Next 24 hours' sedation plan: (Consider dexmedetomidine if agitated delirium present)	