Off-label use of dexmedetomidine in anaesthesiology in South Africa

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Declaration

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

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Dedication

This thesis is dedicated to my family who have been my rock during this journey. To my husband Johan Feuth, my father Johannes Stephanus van Niekerk, my mother Yvonne van Niekerk and my sister Jovonne Cloete, thank you for your unwavering support, patience and love throughout this process.

To my daughter, Vonné Feuth, you are the light of my life and my greatest blessing.

And lastly, to the Almighty Lord, thank you for the strength and guidance throughout this journey

Abstract

Background

Dexmedetomidine is registered for limited use in anaesthesiology and intensive care, however, it is known to be used off-label. The extent of this off-label use in South Africa is not known. This study aims to describe the off-label use of dexmedetomidine in anaesthesiology in South Africa.

Methods

The study was a prospective, contextual, descriptive study using convenience sampling. A self-administered survey was distributed at the national South African Society of Anaesthesiologists Congress as well as the Anaesthetic Foundation Refresher Course in 2018.

Results

A total of 416 surveys were distributed and 188 (45.2%) were returned of which 184 (44.2%) were complete. One hundred and fifty-three (83.2%) participants use dexmedetomidine. Numerous off-label uses of dexmedetomidine were reported including use in the paediatric population (48.4%), as part of a general anaesthetic (54.9%) and as an adjuvant to local anaesthetics in regional (9.4%) and neuroaxial blocks (7.2%). Four participants (2.6%) use dexmedetomidine to decrease spinal shivering while 23.5% use dexmedetomidine to treat emergence delirium. Off-label routes of administration were also identified, namely intranasal (10.5%), intrathecally (5.2%), buccal (2%), intra-articular (1.3%) and subcutaneous (0.65%).

Conclusion

This study has shown that dexmedetomidine is extensively used in adult and paediatric patients by anaesthetists in South Africa. It is also administered via other than the registered intravenous route. Results from this study may stimulate future research that could contribute to the expansion of dexmedetomidine registration.

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Abbreviations

ASA	American Society of Anaesthesiologists
FDA	Food and Drug Administration
ICU	Intensive Care Unit
SAHPRA	South African Health Products Regulatory Authority
SASA	South African Society of Anaesthesiologists

Statement

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

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

Section 2: Review of the literature

2.1 Introduction

Dexmedetomidine is a novel α2-agonist that has found its place in anaesthesiology because of its versatile use and favourable effects. This literature review discusses the regulating bodies responsible for the registration of medication, definition of off-label use, pharmacology and physiological effects of dexmedetomidine, as well as registered and off-label uses of dexmedetomidine.

2.2 Regulating bodies

In the health care industry, it is important to regulate the use of medication in order to ensure both patient safety as well as protecting the physician with regards to legal implications. There are bodies in place to regulate the use of medicines and provide a standard of safety of drugs. A drug needs to be approved by the appropriate governing body before it is allowed onto the market.

The United States of America was the pioneer in drug licensing after adverse events took place with inappropriate prescription of medication. The Food and Drug Administration (FDA) was established in 1906 and functions to determine drug safety and efficacy (1).

In South Africa, the South African Health Products Regulatory Authority (SAHPRA), formerly known as the Medicines Control Council, is the drug licensing authority (2). The Medicines and Related Substances Amendment Act, Act of 2017 was responsible for the change in governing bodies in February 2018 (2). Like the FDA, SAHPRA, regulates the manufacture, distribution, sales and marketing of drugs. The medicines and Related Substances Act is used for the registration of medicine (2). The approval of this drug is indication specific; however, once the drug reaches the market, the drug may be used for other indications other than the original approval (3).

Drug registration is a long, time-consuming and costly process that subjects pharmaceutical products to pre-marketing evaluation, marketing authorisation, and post-marketing review to ensure that they conform to required standards of quality, safety,

and efficacy established by national authorities. The outcome of this process can either be successful or result in denial of a product being registered (4).

2.3 Off-label drug use

“Off-label drug use refers to the prescription of licensed drugs for clinical indications different to that approved by the regulatory authorities and thus not included in the approved labelling for the agents. Use of drugs for a clinical indication, in a patient population, through a route of administration, or with a dose not specified in the governing body labelling can all be considered off-label” (5).

The use of medication for purposes other than the original indication does not imply that it is unsafe or ineffective; off-label use has become mainstream and part of legitimate medical practise across the world. In some instances off-label use can even be considered “state of the art” (2). A study conducted by Carrasco et al (5) in 2001, looked at the prevalence of off-label prescription. It was found that up to 21% of prescriptions do not have FDA-approved indications (5). The use of off-label drugs does not indicate a lack of evidence for their use and drugs are often used off-label in certain population groups such as paediatrics, obstetrics and oncology (5).

There are several benefits of off-label drug use such as the discovery of new treatments that drugs have not been approved for, for example, beta blocker use in heart failure, previously only approved for hypertension, as well as avoidance of the tedious and costly process by relabelling a drug by the FDA (6).

A disadvantage of using any drug for a non-approved indication is that the pharmaceutical company will take no responsibility if any adverse effects arise. Bellis et al (7) showed that there was a 25% increase in adverse events when medications were used off-label.

2.4 Dexmedetomidine

2.4.1 Registration

Dexmedetomidine was approved for use in the United States of America in 1999 and in 2011 in the European Union (8).

Dexmedetomidine is registered in South Africa for use in the intensive care unit (ICU) for sedation and analgesia as well as for conscious sedation in a monitored anaesthetic setting or ICU for minor surgical procedures under local anaesthesia and for fiberoptic intubation (9).

2.4.2 History of dexmedetomidine

The prototype drug clonidine was developed in 1960. The main use of the drug was then as a nasal decongestant due to its vasoconstrictive effects, but from 1966 it was used for its antihypertensive properties. The α2-adreno receptor agonists were originally used to treat patients with hypertension as well as for withdrawal from long term drug and alcohol abuse. These receptor agonists possess diverse characteristics which include anxiolysis, sedation, analgesia and sympatholytic properties (10).

Dexmedetomidine belongs to the imidazole family. It is an α2-adrenoreceptor agonist that has a greater affinity for α2: α1 in a 1620:1 ratio. This compares with clonidine's ratio of 220:1 which is much less selective and specific for α2-adrenoreceptor than dexmedetomidine (11). Due to the unique properties of dexmedetomidine, it is conducive to many anaesthetic applications (12).

2.4.3 Pharmacology

Pharmacokinetics

Dexmedetomidine is metabolised by the liver and undergoes near-complete biotransformation (13). The biotransformation of dexmedetomidine is by means of glucuronidation and cytochrome P450 enzymes in the liver. This metabolism is extensive and decreased doses are required for patients with liver impairment. Elimination is via the renal system as metabolites. Dexmedetomidine follows linear kinetics with a dosage range of 0.2 − 0.7 μg/kg/hr. The clearance is reported at 0.495 L/kg/hr with a volume of distribution at steady state of 1.33 L/kg. The elimination half-life is two hours. Dexmedetomidine has a rapid distribution half-life of six minutes, therefore it has a rapid onset of action making this drug ideal for intravenous use (12).

Due to the rapid distribution and short half-life, dexmedetomidine generally needs to be initiated with a loading dose. For adults the loading dose is usually 1 μg/kg over 10

minutes but can be decreased to 0.5 µg/kg for less invasive procedures. The maintenance dose is 0.2 − 0.7 µg/kg/hr by continuous infusion (9).

A study by Sim et al (14) aimed to describe the effects of different loading doses of dexmedetomidine in forty-six patients who were assigned to either receive a loading dose of 0.5 µg/kg or 1 µ/kg over 10 minutes. In the group that received the higher loading dose, the Bispectral Index was significantly decreased. There was no significant difference between the two groups with regards to vital signs and complications (14). Haemodynamic instability is concern, however, Ramsay et al (15) demonstrated that even at a high maintenance dose of 10µg/kg/hr patients remained haemodynamically stabile. The authors also demonstrated that the respiratory drive was maintained with no need for airway intervention (15).

Pharmacodynamics

Dexmedetomidine exerts its effect via a G-protein coupled mechanism on the pre- and postsynaptic membranes of α2-adrenoreceptors. The α2-adrenoreceptors can be divided into three subtypes; namely α2A, α2B and α2C-adrenoreceptors (12). The alpha subtypes functions are seen Table 1.

Table 1 α2-Adrenoreceptor subtypes and their functions (14, 16)

Receptor subtype	Effect of central and peripheral stimulation
α2A receptor subtype	Sedation Hypnosis Analgesia Sympatholysis Neuroprotection
α2B receptor subtype	Suppress shivering centrally Promote analgesia at spinal cord level Vasoconstriction in peripheral arteries
α2C receptor subtype	Modulates cognition, mood, sensory processing and stimulant-induced locomotor activity Regulates adrenal outflow from the adrenal medulla Inhibition of noradrenaline release (all 3 α - subtypes) Decreased gastrointestinal motility by induction of glucagon release and contraction of gastrointestinal sphincters

The activation of these receptors results in inhibition of noradrenaline release, causing suppression of the sympathetic nervous system leading to sedation, anxiolysis, analgesia and a decrease in blood pressure and heart rate (11). Receptor activation by dexmedetomidine inhibits adenylyl cyclase which causes a decrease in cAMP in the cell as well as an efflux of potassium and inhibition of calcium entry into nerve terminals. These ionic changes cause hyperpolarisation and in turn suppressing neuronal firing in the locus coeruleus and ascending noradrenergic pathway (17). The locus coeruleus is a key modulator for α2-adrenoreceptor activity and is a role player in brain functions such as anxiety, arousal, sleep and withdrawal of central nervous system-depressant-drugs such as opioids (12).

The different subtypes of the α2-adrenoreceptor have different effects when activated. Stimulation of the α2A-adrenoreceptor subtype mediates the effect of sedation and analgesia, while stimulation of the α2B-adrenoreceptor subtype causes vasoconstriction which leads to the initial hypertensive effects. The α2C-adrenoreceptor is responsible for dopaminergic transmission, hypothermia and various behavioural responses (12).

Dexmedetomidine exerts a non-GABAergic effect as well as an effect from site specific binding. This is characterised by a calm state that is easily rousable to verbal command and renders the patient cooperative to commands or instructions (8). This profile has made dexmedetomidine amenable to a variety of anaesthetic uses that are not limited to sedation (12), such as intrathecal anaesthesia, local and regional anaesthesia, intra-articular injection, as an adjunct to general anaesthesia and for conscious sedation among others (13). Dexmedetomidine also has properties that render the drug neuro- and cardioprotective (18, 19). The side effects of dexmedetomidine include hypotension, hypertension, bradycardia, nausea and vomiting, fever and tachycardia (20).

2.4.4 Physiological effects of dexmedetomidine

The mechanism of analgesia of dexmedetomidine is mediated via activation of the α2A-adrenoreceptors which leads to potassium efflux from the Gi-protein-gated-potassium channels in the neuron thereby causing hyperpolarisation and in turn suppressing neuronal firing (18, 21, 22). Central and peripheral α2A-adrenoreceptors are the preferential binding sites of dexmedetomidine and these, along with spinal and supraspinal receptors are responsible for analgesia (18, 21, 23). Stimulation of the presynaptic receptor inhibits transmitter release from primary afferent fibres, while postsynaptic stimulation at the level of the spinal cord increases acetylcholine in the superficial dorsal horn. In turn, this action decreases the release of neurotransmitters such as glutamate and substance P, leading to inhibition of nociceptive neurotransmission (21).

Dexmedetomidine has significant opioid sparing effects as well as decreasing the requirements for inhalational agents (24). It can decrease anaesthetic requirements by up to 90% while simultaneously having an analgesic effect (25). One of the mechanisms

by which dexmedetomidine has an analgesic effect is via synergising opioid receptor agonists, systemically and locally (21).

During the perioperative period the body exerts a stress response which is characterised by an increase in sympathetic activity. This leads to tachycardia and hypertension which can influence oxygen supply-demand balance negatively. Attenuation of this response through administration of dexmedetomidine, can lead to haemodynamic stability and hence a decrease in perioperative ischaemic episodes as well as being cardioprotective during episodes of ischaemia (11, 26, 27).

Dexmedetomidine is cardioprotective as it protects against ischaemia-reperfusion injury. One mechanism is via activation of the BKca channels which is an essential signalling pathway of cardioprotective mechanisms (28). A further effect is related to a decrease in noradrenaline release through blunted central sympathetic activity. This leads to haemodynamic stability and better myocardial oxygen balance. Dexmedetomidine generates nitric oxide via the eNOS-dependent mechanism and this is also cardioprotective (13, 28).

Dexmedetomidine has also been shown to be neuroprotective (13, 17). It is a promising drug in neurosurgery as it provides haemodynamic stability (13). This is important in attenuating the precipitous rise in intracranial pressure during both intubation and extubation. Dexmedetomidine attenuates neurocognitive impairment thus decreasing the incidence of postoperative delirium (27).The anti-inflammatory effect of dexmedetomidine is considered to be part of the mechanism involved in neuroprotection from cerebral ischaemia/reperfusion injury (13).

A study by Kim et al (19) on rats, aimed to investigate the neuroprotective effects of dexmedetomidine. This study concluded that administration of dexmedetomidine prior to an ischaemic event inhibited inflammation by decreased TLR-4/NF-KB expression and decreased production of pro-inflammatory cytokines. They also demonstrated less apoptosis via decreasing caspase-3 expression after transient global cerebral ischaemia-reperfusion injury (19). Sanders et al (29) demonstrated that dexmedetomidine, in combination with an isoflurane anaesthetic significantly reduced apoptosis of the hippocampal cells in newborn rat pups.

2.4.5 Clinical applications of dexmedetomidine

Dexmedetomidine is used for both registered as well as off-label uses.

Registered use

Dexmedetomidine is often used for sedation in the anaesthetic setting due to its favourable profile as a non-respiratory depressant. A case report by Rich (20) aimed to determine the efficacy of dexmedetomidine as a sole sedating agent for an axillofemoral bypass graft. The patient, a 70-year-old male with debilitating comorbidities would likely not survive postoperative ventilation in the event of inability to wean off the ventilator; therefore, local anaesthesia with sedation was used. A 1 µg/kg loading dose of dexmedetomidine was used followed by an infusion up to 0.7 µg/kg per hour achieving an adequate level of sedation for the surgery to proceed under local anaesthetic with lignocaine. The sedation with dexmedetomidine was found to be adequate (20).

Wang et al (30) compared dexmedetomidine (DEX group) to propofol (PRO group) for sedation in patients undergoing inguinal hernia repair under local anaesthesia. The study was a prospective randomised control trial of 80 patients. The patients in the DEX group received a loading dose of 0.5 µg/kg over 10 minutes followed by an infusion of 0.5 µg/kg/hr until the end of the surgery. The patients in the PRO group received a loading dose of propofol at 2 mg/kg over 10 minutes followed by an infusion of 1.5 mg/kg/hr until the end of surgery. The target of sedation was a Ramsay sedation score of 3. Infusion doses were adjusted either by 20% increase or decrease depending on the level of sedation. All patients received 0.5 µg/kg of fentanyl five minutes prior to surgical incision. Patients underwent local infiltration of lidocaine superficially followed by a regional block with ropivacaine. Fentanyl boluses were added if the patient moved due to pain or complained of pain. The intraoperative requirements for fentanyl were significantly lower in the DEX group and this group had a lower pain score postoperatively. The time to onset of sedation and recovery from sedation was slightly longer in the DEX group (30).

Awake fiberoptic intubation is indicated in many anaesthetic scenarios and can prove to be very challenging (30). Patient preparation is key, and success depends on a cooperative, well anxiolysed patient that can still obey commands while being sedated.

An important consideration for awake fiberoptic intubation is maintenance of a patent airway at all times to ensure ventilation, loss of spontaneous respiration would be catastrophic. Therefore, one needs to sedate while maintaining a patent airway. Drugs that are often used include propofol, benzodiazepines and opioids which all have limitations with regards to their side effects, such as respiratory depression and possible loss of the patent airway (30).

Bergese et al (31) described four case studies on patients with difficult airways, evaluating dexmedetomidine for conscious sedation in awake fiberoptic intubation. They describe the ideal sedative as a drug that will “allow the patient to maintain spontaneous ventilation and protect their own airway”. The drug must allow the patient to be cooperative and rousable and still tolerate the passage of the fiberoptic scope. Four patients with difficult airways received a dexmedetomidine loading dose of 1 µg/kg intravenously over 10 minutes followed by a continuous infusion at 0.5 µg/kg/hr. In all the patients, dexmedetomidine provided adequate sedation and optimal conditions for awake fiberoptic intubation. All patients were cooperative and experienced no discomfort while remaining haemodynamically stable (31).

In a similar study by Abdelmalak et al (32), dexmedetomidine was used as the sole sedating agent for intubation in patients with a critical airway. A critical airway is a life-threatening scenario of hypoxemia which could lead to hypoxia, following failed or inadequate ventilation. Five patients were used as case studies. All five patients underwent topicalisation of the oropharynx with nebulized 4% lidocaine and 2% lidocaine gel and a loading dose of dexmedetomidine was initiated at 1 µg/kg followed by an infusion of 0.6 µg/kg/hr. All patients tolerated the intubation well with minimal discomfort (32).

Similarly, a study in China looked at the comparison between dexmedetomidine-midazolam and sufentanil-midazolam combination for awake fiberoptic nasotracheal intubation. The study consisted of 50 patients that were randomised into two groups of 25 patients each. Both groups received midazolam as a premedication and airway topicalization. Dexmedetomidine was given at a loading dose of 0.5 µg/kg over 10 minutes followed by an infusion of 0.25 µg/kg/hr. The sufentanil group received a loading dose of 0.2 µg/kg over 10 minutes followed by an infusion of 0.1 µg/kg/hr. Both groups had comparable scores with regards to the ease of the procedure, coughing,

tolerance of intubation, recall of the procedure and discomfort, however, the first partial pressure of carbon dioxide directly after intubation was higher in the sufentanil group indicating a higher degree of respiratory depression (33).

Off-label use

Different off-label routes of administration and applications (including the paediatric population) of dexmedetomidine is described extensively in the literature.

Paediatrics, intranasal, buccal and intramuscular

There is literature available on dexmedetomidine sedation in the paediatric population (11, 34-42). Unfortunately this drug is not registered for the paediatric population despite evidence of its benefits (9). A systematic review and meta-analysis of paediatric patients were conducted on the efficacy of sedation with intranasal dexmedetomidine compared with other agents and other modes of administration. The meta-analysis included eleven randomized control trials. The search found that intranasal dexmedetomidine was associated with more superior sedative effects compared with oral benzodiazepines, however, there was a significant delayed onset of action (38). Identical results were found by another systematic review of 13 studies (1,168 participants) on the adequacy of intranasal dexmedetomidine premedication in children (43).

Sheta et al (44) compared intranasal dexmedetomidine with intranasal midazolam in children undergoing complete dental extraction. Seventy-two children were enrolled aged 3 - 6 years. The children were randomly assigned to either intranasal dexmedetomidine (1 µg/kg) or intranasal midazolam (0.2 mg/kg). The results demonstrated that the median onset time for sedation was shorter in the midazolam group 15 (10-25 IQR) min compared to dexmedetomidine 25 (20-40 IQR) min. The children who received dexmedetomidine were significantly more sedated at time of parental separation. Satisfactory compliance with mask acceptance was 58.3% in the midazolam group and 80.6% in the dexmedetomidine group and the incidence of postoperative shivering and agitation was lower in dexmedetomidine group. The midazolam group experienced significant nasal irritation (36.1%) compared with no children exhibiting these signs in the dexmedetomidine group. There was no incidence

of adverse effects in the dexmedetomidine group and both groups remained haemodynamically stable throughout (44).

Cimen et al (45) demonstrated that 1 µg/kg intranasal dexmedetomidine was more effective than buccal administration of dexmedetomidine at the same dose. Levels of sedation, parenteral separation and acceptance of mask was significantly higher in the intranasal group.

A study by Shi et al (46) aimed to determine whether intravenous dexmedetomidine was preventative for emergence delirium and postoperative behavioural changes in paediatric patients receiving sevoflurane anaesthesia. Patients aged 2 – 7 years, undergoing tonsillectomy were randomly assigned to receive either dexmedetomidine 0.5 µg/kg or volume-matched normal saline over 10 minutes after induction of anaesthesia. The primary outcome was the incidence of emergence delirium within 30 minutes after extubation. Other outcomes included the incidence of pain, extubation time, postanaesthesia care unit length of stay after extubation, adverse events and the incidence of negative postoperative behavioural changes. Ninety children were enrolled in the study. Dexmedetomidine decreased the incidence of emergence delirium (31.1% vs 53.3%; P=0.033) and pain (28.9% vs 57.8%; P=0.006), but it prolonged extubation time (P=0.001). Post anaesthesia care unit length of stay after extubation and the percentage of adverse events were similar between groups. The incidence of negative postoperative behavioural changes in the dexmedetomidine group at day 1 and 7 after discharge was significantly lower (33.3% vs 60.0%; P=0.011% and 24.4% vs 46.7%; P=0.028, respectively) than in the control group (46).

Intrathecal, intra-articular injection and intramuscular

A study by Sun et al (47) found that intramuscular dexmedetomidine (1 µg/kg) as a premedication provides satisfactory sedation as well as decreased anaesthetic requirements for patients undergoing suspension laryngoscopic surgery.

Many studies have demonstrated the use of dexmedetomidine intrathecally (42, 48-53). Ismail et al (50) examined the difference between intrathecal and intra-articular dexmedetomidine compared with a control group in patients undergoing knee arthroscopy. The study's main objective was to look at differences in pain and analgesic requirements postoperatively. There were 90 patients in total, divided into three groups

of 30 patients in each group. The groups were divided as follows; a group that received intrathecal dexmedetomidine over and above the bupivacaine dose; a group that received intra-articular dexmedetomidine and a group that received a placebo. All the surgeries were performed under spinal anaesthesia and there was no significant difference with regards to the patient demographics. The study found that in both the intrathecal and intra-articular dexmedetomidine group the pain scores were lower post operatively, while maintaining haemodynamic stability (50).

There have been studies looking at the effect of intrathecal dexmedetomidine on shivering in spinal anaesthesia (49, 53, 54). He et al (49) demonstrated that intrathecal dexmedetomidine at a dose of 5 µg added to hyperbaric bupivacaine for spinal anaesthetic for caesarean section decreased shivering significantly compared to both placebo and dexmedetomidine at a dose of 2.5 µg (49).

A similar study enrolled 54 patients for elective caesarean section undergoing spinal anaesthesia (53). Two groups were randomly assigned with 27 patients in each group receiving either 5 µg of dexmedetomidine or 0.5 ml normal saline in conjunction with 12.5 mg 0.5% heavy bupivacaine. The results indicated a significant difference in both occurrence (52% versus 24%) and intensity of shivering, while there was no significant difference with regards to haemodynamic parameters between the two groups (53).

Regional blocks

Studies have been performed to determine the effect of dexmedetomidine as an adjunct to local anaesthetics (55-59). Nazir and Jain (59) studied the effect of dexmedetomidine added to bupivacaine for ultrasound guided supraclavicular blocks. Two groups were randomised in a double-blind study with 70 American Society of Anaesthesia (ASA) 1 and 2 patients; each group consisted of 35 patients. Patients were assigned to receive either 2 ml normal saline or 1µg/kg dexmedetomidine (2ml) as adjuvants to 38ml of 0.25% bupivacaine. The dexmedetomidine group demonstrated a significantly faster onset of action and longer duration of action. There was no significant haemodynamic change and no adverse effects were reported (59).

In another study, similar effects were reported with 60 ASA 1, 2 and 3 patients randomly assigned to receive 30 ml of 0.5% ropivacaine, with either 1 ml normal saline or 1 ml of 1 µg/kg dexmedetomidine added to the local anaesthetic. Onset of action was faster

with a longer duration of action in the dexmedetomidine group compared to the control group (55).

In contrast to the above studies, dexmedetomidine added to ropivacaine for transverse abdominal plane blocks did not seem to have any significant effect on the quality of the block in a study on patients receiving this block for gastrectomy (56).

Intravenous regional anaesthesia is often used for short duration forearm and hand surgeries. One study demonstrated that addition of dexmedetomidine to lignocaine had a significant effect on various outcomes of the anaesthetic. Thirty patients for hand surgery were randomly assigned to two groups. Both groups received 40 ml of 0.5% lignocaine with the addition of either 1 ml isotonic saline or 1 ml of 0.5 µg/kg dexmedetomidine in combination with the lignocaine intravenously. The study found the following: the dexmedetomidine group had shorter onset of motor and sensory block times, longer duration of block, prolonged tolerance of tourniquet and a decreased need for adjunctive analgesics (25).

Dexmedetomidine in conjunction with local anaesthetics in wound infiltration has been found to increase the analgesic effect. Infiltration with ropivacaine and dexmedetomidine at the skin incision site in laparoscopic cholecystectomy yielded significant difference from infiltration with ropivacaine alone. It was found that patients experienced less pain, needed less meperidine postoperatively and slept better during the first night after surgery in addition to being mobile sooner (58).

Postoperative delirium

Emergence delirium and postoperative delirium is a commonly encountered postoperative complication and is associated with morbidity as well as increased hospital stay. Emergence delirium is characterised by an acute change in cognition with fluctuating consciousness and attention due to the administration of anaesthesia, occurring in the immediate postoperative recovery period (60). There is sufficient evidence to suggest that dexmedetomidine can attenuate the occurrence of emergence delirium (5, 60-66). Read et al (60) reported, in a case study of three patients with postoperative emergence delirium, that dexmedetomidine was effective in alleviating postoperative emergence delirium (60). Postoperative delirium is a neurobehavioral syndrome secondary to transient disruption of normal neuronal activity due to systemic

disturbances (67). Maldonado et al (67) investigated the development of postoperative delirium in a group of patients that were undergoing cardiac surgery. Patients were randomly assigned to receive one of three postoperative sedatives namely propofol, dexmedetomidine or midazolam. The incidence of delirium was significantly lower in the group that received dexmedetomidine (3%) versus 50% for both the propofol and midazolam groups. This is a significant finding as patients with postoperative delirium have a longer hospital stay especially in the ICU and this is associated with significant health care costs (67).

2.5 Research on off-label use

The research on dexmedetomidine and its off-label use is limited. Only one study could be found. This study was done two years after the registration of dexmedetomidine in Europe in 2011. This may explain the reason why results demonstrated that dexmedetomidine is generally used within its registered indications.

The study was a 2000 patient multinational drug utilisation study, done in Europe, to investigate how dexmedetomidine is used in clinical practice with specific emphasis placed on the so called off-label uses. The study was conducted in 18 institutions in Finland, Poland, Austria and Germany between June 2013 and December 2014. The patient data was collected retrospectively and comprised of patient demographics, dexmedetomidine dose and duration of infusion and setting (ICU, theatre, ward) in which dexmedetomidine was administrated. The most frequent indication for use was ICU sedation (78.6%), perioperative use (15.5%) and procedural sedation (5%). The study concluded that the majority of dexmedetomidine use was within the limits of the product labelling. The use in the paediatric population was limited, but mostly within the scope of the adult population (8).

2.6 Summary

Dexmedetomidine is extensively researched in the literature for various applications. It is unfortunate that this versatile drug is registered for limited indications. Many more large studies need to be done in order to ensure safe use of the drug with regards to off-label use, but as demonstrated by the literature dexmedetomidine is a novel agent that has the potential to change our anaesthetic practice for the better.

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Acknowledgements

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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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Section 4: Draft article

Off- label use of dexmedetomidine in Anaesthesiology in South Africa

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Keywords: Dexmedetomidine, off-label use

Abstract

Background

Dexmedetomidine is registered for limited use in anaesthesiology and intensive care, however, it is known to be used off-label. The extent of this off-label use in South Africa is not known. This study aims to describe the off-label use of dexmedetomidine in anaesthesiology in South Africa.

Methods

The study was a prospective, contextual, descriptive study using convenience sampling. A self-administered survey was distributed at the national South African Society of Anaesthesiologists congress as well as the Anaesthetic Foundation Refresher Course in 2018.

Results

A total of 416 surveys were distributed and 188 (45.2%) were returned of which 184 (44.2%) were complete. One hundred and fifty-three (83.2%) participants used dexmedetomidine. Numerous off-label uses of dexmedetomidine were reported including use in the paediatric population (48.4%), as part of a general anaesthetic (54.9%) and as an adjuvant to local anaesthetics in regional (9.4%) and neuroaxial blocks (7.2%). Four participants (2.6%) used dexmedetomidine to decrease spinal shivering while 23.5% used dexmedetomidine to treat emergence delirium. Off-label routes of administration were also identified, namely intranasal (10.5%), intrathecal (5.2%), buccal (2%), intra-articular (1.3%) and subcutaneous (0.65%).

Conclusion

This study has shown that dexmedetomidine is extensively used in adult and paediatric patients by anaesthetists in South Africa. It is also administered via other than the registered intravenous route. Results from this study may stimulate future research that could contribute to the expansion of dexmedetomidine registration.

Introduction

Regulation of medication in the health care industry is pivotal in order to ensure the safety of patients. It also functions to protect the physician should adverse events following prescription and administration of medication occur. [1] In South Africa, the South African Health Products Regulatory Authority, formerly known as the Medicines Control Council, is responsible for the regulation of medication.

"The term 'off-label' means that the medicine is used in another way than specified in the conditions of registration of the medicine and as reflected in its labelling".[1] The use of drugs off-label is not illegal; it is often a necessity in certain population groups such as paediatrics, oncology and obstetrics where ethical dilemmas hinder clinical trials.[1, 2] Using drugs off-label can range from being standard practice to experimental. However, it is important to note that Bellis et al [3] demonstrated a 25% increase in adverse events when medications were used off - label.

Dexmedetomidine is registered in South Africa for use in intensive care for sedation and analgesia as well as for conscious sedation, in a monitored anaesthesia setting or intensive care, for minor surgical procedures under local anaesthesia and for fiberoptic intubation.[4] Numerous other uses have been reported, especially in the anaesthetic setting [5-8] and include use in conjunction with local anaesthetic agents, in intrathecal injections [9-12] and regional blocks such as supraclavicular blocks, transabdominal plane blocks and local infiltration.[13-17] It has also been used for sedation, anxiolysis and analgesia in the perioperative period.[8, 18-33] Other off-label uses include treatment or prevention of postoperative shivering [34-36] and postoperative delirium,[37-42] intra-articular injection to minimise postoperative pain, [12] use in intramuscular injection [43-45] as well as use in the paediatric population. [19, 26, 27, 32, 46, 47]

Dexmedetomidine has also shown to be both neuro- and cardioprotective. [28, 32, 33, 48-50] The added benefit of haemodynamic stability and rapid emergence is promising for neurosurgery where sudden increases or decreases in blood pressure are to be avoided and early neurological evaluation is essential. [7]

Using medication off-label has implications, not only for the patient, but for the health care professional as well. Due to advertising and marketing restrictions imposed on pharmaceutical companies regarding off-label use of drugs, it is not known to what extent dexmedetomidine is used off-label in South Africa. Jansen [1] suggests that research is generated through the medical

community, therefore the onus is on the medical community to establish the extent to which a medication is used. This study aims to describe the off-label use of dexmedetomidine in anaesthesiology in South Africa.

Methods

A prospective, contextual, descriptive research design was followed. Approval to conduct this study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand and other relevant authorities.

The study population consisted of anaesthetists attending the annual national South African Society of Anaesthesiologists Congress in April 2018 and the Anaesthetic Foundation Refresher Course in September 2018. A convenience sampling method was used. The data were collected with an anonymous self-administered survey. The sample size was realised by the number of surveys returned.

The survey was compiled after reviewing the literature, thereby ensuring content validity. The draft survey was reviewed by five specialist anaesthetists in the Department of Anaesthesiology at the University of the Witwatersrand and their comments were included in the final survey, thereby ensuring content and face validity. Section 1 of the survey included demographic data and Section 2 consisted of 10 questions regarding the use of dexmedetomidine.

Participation in the study was voluntary and consent was implied by completion of the survey. Anonymity and confidentiality were maintained by not requesting identifying information. The surveys were returned to sealed data collection boxes. One author, (MF), was available to address any questions. Data were entered onto a spreadsheet and analysed using descriptive statistics. Categorical variables were described using frequencies and percentages.

Results

At the congresses, a total number of 416 surveys were distributed and 188 (45.2%) were returned. Four blank surveys were excluded resulting in a sample realisation of 184 (44.2%). The characteristics of the participants is shown in Table I.

Table I Characteristics of participants

Characteristic	Number	Percent
Gender		
Male	109	59.2
Female	75	40.8
Age		
25 – 35 years	51	27.7
36 – 45 years	69	37.5
46 – 55 years	28	15.2
> 55 years	35	19.0
Sector		
Public	70	38.0
Private	87	47.3
Public and Private	27	14.7
Professional designation		
General practitioner	4	2.2
Diploma anaesthetist	7	3.8
Registrar	43	23.4
Specialist anaesthetist	130	70.7
Anaesthetic experience		
< 5 years	27	14.7
5 – 10 years	59	32.1
> 10 years	98	53.3

A total of 175 (95.1%) participants completed the question regarding the definition of off-label drug use. The majority, 143 (77.7%), answered correctly. One hundred and fifty-three (83.2%) participants use dexmedetomidine in their anaesthetic practise. Of the participants who use dexmedetomidine, 79 (51.6%) use it in the adult population only, 8 (5.2%) in the paediatric population only and 66 (43.1%) in both adults and paediatrics. The frequency of use of dexmedetomidine is summarised in Table II. Due to dexmedetomidine being used by anaesthetists in both the public and private sector at different frequencies, the numbers total more than the number of anaesthetists who use the drug.

Table II Frequency of use of dexmedetomidine in anaesthetic practice

Dexmedetomidine use	**Sector n (%)**			
	Total	**Public**	**Private**	**Both**
Yes	153 (100)	58 (37.9)	79 (51.6)	16 (10.4)
Frequency of use				
Almost every anaesthetic	1 (0.65)	1 (0.65)	0	0
At least once daily	14 (9.2)	2 (1.3)	11 (7.2)	1 (0.65)
At least once weekly	44 (28,8)	15 (9.8)	27 (17.6)	2 (1.3)
Occasionally	126 (82.4)	64 (41.8)	48 (31.4)	14 (9.2)

The different routes of dexmedetomidine administration and the sector where it was used are shown in Table III. The 2 (1.3%) participants stating “other” use the drug in paravertebral and caudal blocks.

Table III Routes of dexmedetomidine administration

Route	**Sector n (%)**		
	Public	**Private**	**Both**
Intravenous	62 (40.5)	75 (49)	16 (10.5)
Intranasal	16 (10.5)	20 (13.1)	2 (1.3)
Intrathecal	2 (1.3)	6 (3.9)	0
Buccal	3 (2)	5 (3.3)	0
Subcutaneous	0	1 (0.65)	0
Intra-articular	1 (0.65)	1 (0.65)	0
Other	2 (1.3)	0	0

The use of dexmedetomidine and the sector where it was used are shown in Table IV.

Table IV Uses of dexmedetomidine

Procedures/indication	Sector n (%)			
	Total	Public	Private	Both
Conscious sedation in theatre	108 (70.6)	49 (32)	52 (34)	7 (4.6)
Sedation and analgesia in intubated ICU patients	93 (60.8)	30 (19.6)	56 (36.6)	7 (4.6)
Sedation and analgesia in non-intubated ICU patients	71 (46.4)	13 (8.5)	55 (35.9)	3 (2)
Awake fiberoptic intubation	81 (53)	42 (27.5)	36 (23.5)	3 (2)
Part of a general anaesthetic	84 (54.9)	30 (19.6)	48 (31.4)	6 (3.9)
Paediatric anaesthesia including premedication	70 (45.8)	36 (23.5)	32 (20.9)	2 (1.3)
Treatment of delirium and emergence delirium	36 (23.5)	12 (7.8)	23 (15)	1 (0.65)
Local anaesthetic adjunct in regional anaesthesia	14 (9.2)	6 (3.9)	8 (5.2)	0
Local anaesthetic adjunct in neuraxial anaesthesia	11 (7.2)	5 (3.3)	6 (3.9)	0
Decrease spinal shivering	4 (2.6)	1 (0.65)	3 (2)	0
Intra-articular injection	1 (0.65)	0	1 (0.65)	0

Of the 153 participants who use dexmedetomidine, 113 (73.9%) used a loading dose. The loading doses and maintenance doses used are shown in Table V.

able V Dexmedetomidine loading and maintenance doses

Loading dose	**Number**	**Percentage**
0.1 – 0.5 µg/kg over 10 minutes	23	20.4
0.5 – 1 µg/kg over 10 minutes	61	54
1 – 2 µg/kg over 10 minutes	24	21.2
Other	5	4.4
Maintenance dose		
< .2 µg/kg/hr	139	90.8
0.2 − 0.7 µg/kg/hr	6	3.9
> 0.7 µg/kg/hr	8	5.2

Only 26 (65%) of the 40 participants who do not use a loading dose gave a reason. Reasons for not using a loading dose are shown in Table VI.

Table VI Reasons for not using a loading dose of dexmedetomidine

Reason	**Number**	**Percentage**
Haemodynamic instability	7	17.5
Used for ICU sedation only	6	15
Used as part of multimodal analgesia	5	12.5
Titrated to effect	4	10
Rapidly reaches therapeutic level	1	2.5
Unnecessary	1	2.5
Apnoea	1	2.5
Not recommended	1	2.5

Discussion

The study aimed to determine how anaesthetists use dexmedetomidine in South Africa with specific emphasis on off-label use. The only similar study identified is the 2013–2014 European retrospective multinational drug utilisation study conducted in 18 institutions in Finland, Poland, Austria and Germany. [51] At the time of the study dexmedetomidine was registered for sedation of adults in intensive care only. [51] This is different from the current registration in South Africa, which includes sedation for minor surgical procedures as well as for use in sedation in awake fiberoptic intubation. Dexmedetomidine is also only registered for intravenous use. [4]

The European study [51] found that the most frequent indications for use were ICU sedation (78.6%), perioperative use, defined as "improving emergence from anaesthesia and sedation during regional anaesthesia" (15.5%) and procedural sedation (5%). [51] In our study, the use for sedation and analgesia in ICU was 60.8% and 46.4% for intubated and non-intubated patients, respectively, while 70.6% of participants use dexmedetomidine for conscious sedation in theatre and 54.9% use it as part of a general anaesthetic. This demonstrates the different uses of dexmedetomidine between the two studies. A possible reason for the substantial difference, may be because the European study was done only two years after dexmedetomidine registration, therefore, use was mainly found to be within the limits of registration. Studies [18, 52-54] have demonstrated that dexmedetomidine is an ideal drug for concious sedation in awake fiberoptic intubation. This is also demonstrated in our study with 52.9% of participants reporting using the drug for this indication.

Although dexmedetomidine is not registered for paediatric use, there are numerous studies demonstrating its use in this population, [23, 26, 27, 40] which include use in caudal blocks [46, 47, 55] and intranasal administration for sedation. [56-59] There was a noteworthy difference in the use of dexmedetomidine in paediatric patients between our study and the European study. The European study [51] found a prevalence of only 5.9% use in paediatrics as opposed to 48.4% demonstrated in our study. Intranasal and buccal dexmedetomidine is used by 24.8% and 5.2% of the participants respectively and one used dexmedetomidine in caudal blocks.

As opposed to the European study [51] where all use was intravenous, our study identified other routes of administration of dexmedetomidine. Dexmedetomidine has been used intrathecally to decrease spinal shivering [34-36] as well as to augment spinal analgesia. [9-11] Dexmedetomidine was used by 2.6% of participants to decrease spinal shivering and by 7.2% as adjunct in neuroaxial

anaesthesia. Intra-articular dexmedetomidine was found to be superior in analgesic effect to intrathecal dexmedetomidine in a study by Ismail et al. [12] In our study, 1.3% of participants use dexmedetomidine in intra-articular injections. Studies have been performed to determine the effect of dexmedetomidine as an adjunct to local anaesthetics [13-16, 60] for regional blocks. Our study found that 9.2% of participants use dexmedetomidine in this manner. Dexmedetomidine has also succesfully been used as either a treatment modality for postoperative emergence delirium or to prevent delirium. [37-40, 42] In our study, dexmedetomidine was used by 23.5% of participants to treat delirium/emergence delirium.

The majority of participants in our study, 82.4%, use dexmedetomidine occasionally while 28.8% use it at least weekly. Our study examined both private and public sector use as the expense of the drug and the availability in the public sector may influence frequency of use. Participants may, for example, use dexmedetomidine weekly in public, but daily in private, therefore the total numbers do not add up to the total of participants that use dexmedetomidine.

The recommended loading dose of dexmedetomidine is 1 µg/kg over 10 minutes and the maintenance dose 0.2 − 0.7 µg/kg/hr. [4] The European study found that less than 2% of participants used a loading dose, this may be due to the majority of use being in ICU and time can be allowed to reach therapeutic levels, therefore, a maintenance infusion will suffice. Our study found that 73.9% of participants use a loading dose. Fifty-four percent use a loading dose within the prescribed range of 0.5 – 1 µg/kg. Sixty-five percent of the participants who do not use a loading dose supplied a reason for this. Haemodynamic instability was the most common reason (17.5%). Ramsay et al [61] used dexmedetomidine for a total intravenous anaesthetic and reported maintenance dosages of up to 10 µg/kg/hr were tolerated without significant negative haemodynamic effects. Their findings as well as other literature demonstrates that the respiratory drive was maintained even at this high dose. [5, 7, 61, 62] In our study, one participant reported apnoea as a side effect, however, this is not in keeping with the favourable side effect profile and lack of respiratory depression reported with dexmedetomidine use. A loading dose is recommended for dexmedetomidine to achieve an initial fast onset of sedation unless in a setting where the patient is already sedated. [8] This is in contrast with one participant who suggested that a loading dose is not recommended.

Conclusion

Jansen et al [1] suggests that research is generated through the medical community and therefore the responsibility rests on the medical community to determine the off-label uses of drugs. This study has shown that dexmedetomidine is extensively used in adult and paediatric patients by anaesthetists in South Africa. It is also administered via other than the registered intravenous route. Results from this study may stimulate future research that could contribute to the expansion of dexmedetomidine registration.

Conflict of interest

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

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Section 5: Proposal

Off-label use of dexmedetomidine in anaesthesiology in South Africa

Margarethe Feuth

1537445

Supervisor:	Juan Scribante
	Department of Anaesthesiology
Co-supervisor:	Helen Perrie
	Department of Anaesthesiology
Co-supervisor:	Chris Anamourlis
	Department of Anaesthesiology

5.1 Introduction and problem statement

Regulation of medication in the health care industry is pivotal in order to ensure safety of patients. It also functions to protect the physician from legal implications that may arise from adverse events following prescription and administration of medication (1).

The United States of America was the first to establish a council in order to regulate medication use; this governing body is known as the Food and Drug Administration (FDA). They scrutinise new drugs and approve these drugs for specific indications based on research and clinical trials (2). In South Africa, the South African Health Products Regulatory Authority (SAHPRA), formerly known as the Medicines Control Council is responsible, among other things, for the regulation of medication. The Medicines and Related Substances Amendment Act 14 of 2015 (3) was officially passed in June 2017 which governed the change of the regulatory body (1).

“The term ‘off-label’ means that the medicine is used in another way or for an indication other than those specified in the conditions of registration of the medicine and as reflected in its labelling” (1). The use of drugs off-label is not illegal; in fact, it is often a necessity in certain population groups such as paediatrics, oncology and obstetrics where ethical dilemmas hinder clinical trials. Off-label use can vary from being standard practice to experimental. It remains unethical to use drugs that are not tested, keeping in mind that anecdotal data are not equivalent to clinical trials (4).

Dexmedetomidine is a highly selective and potent α2-adrenoreceptor agonist with sedation, analgesia, amnesia and sympatholytic properties (5). Dexmedetomidine has cardiovascular effects and the haemodynamic consequences of administration have been reported in the literature (6-10). There are studies which examine the possible neuro- and cardioprotective effects of dexmedetomidine (11, 12). Although the main route of administration is via intravenous injection, other routes have been described, namely intranasal (13), intrathecal, subcutaneous and buccal (14). It is because of the combination of the above mentioned properties that dexmedetomidine has found a place in anaesthesiology (5).

Dexmedetomidine is currently registered for use in the intensive care for sedation and analgesia as well as for conscious sedation in a monitored anaesthetic or intensive care setting for minor surgical procedures under local anaesthesia and for fiberoptic

intubation (15). Following a review of the literature numerous other uses have surfaced, especially in the anaesthetic setting (5). According to the literature, dexmedetomidine has been used in conjunction with local agents in intrathecal injections (16-19) and regional blocks such as supraclavicular blocks, transabdominal plane blocks and local infiltration (20-24). It has also been used as an adjunct for sedation, anxiolyses and analgesia in the perioperative period (8, 25-40). Other uses include treatment of postoperative shivering (17, 19) and postoperative delirium (41-43), as well as intra-articular injection to minimise postoperative pain (18).

5.2 Aim and objectives

5.2.1 Aim

The aim of this study is to describe the off-label use of dexmedetomidine in anaesthesiology in South Africa.

5.2.2 Objectives

The primary objectives of this study are to**:** The objectives of this study are to:

- describe the procedures/indications dexmedetomidine is used for
- describe the different routes of administration of dexmedetomidine
- describe the use of loading dosages for dexmedetomidine
- describe the dosages that are used for the different indications/procedures
- determine anaesthetists understanding of off-label use.

5.3 Research assumptions

The following definitions will be used in this study.

Specialist anaesthetist: an anaesthetist who has successfully completed all the College of Anaesthesiology examinations, or equivalent, and meets all the criteria to become a specialist (46).

General practitioner: a qualified medical doctor who has no additional training in anaesthesiology. The practice of anaesthesiology by this medical practitioner is not recommended unless in dire emergency cases (46).

Specialist in training/registrar: a qualified doctor who is registered with the Health Professional Council of South Africa as a trainee anaesthetist. This designation of doctors is to practice under supervision at all times (46).

Diploma anaesthetist: a qualified doctor practising anaesthetics who has a Diploma in Anaesthesiology (DA) from the College of Anaesthesiology, these medical practitioners are able to practice independently for American Society of Anaesthesiologists Class (ASA) 1 and ASA 2 patients (46).

Clinical Associates: a category of health professionals that assess patients, make diagnoses, prescribe treatment and perform minor surgery under the supervision of a physician (47).

Paediatric patient: a child under the age of 12 years.

5.4 Demarcation of study field

The study will be conducted at the annual national South African Society of Anaesthesiologists (SASA) Congress held in Cape Town from 4 -8 April 2018 (will be referred to as the SASA 2018 Congress) as well as at the Anaesthetic Foundation Refresher Course in 2018.

SASA is an association that has existed since 1948. This association is devoted to the welfare of its members and seeks to advance the discipline of anaesthesiology at an academic as well as a clinical level (46).

5.5 Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduates Studies Committee of the University of the Witwatersrand.

Approval to conduct the study will also be obtained from the chair of the organizing committee of the SASA 2018 Congress (Appendix 1) and Anaesthetic Foundation Refresher Course 2018 (Appendix 2).

Delegates of the SASA 2018 Congress and the Anaesthetic Foundation Refresher Course will be invited (Appendix 3: Information sheet) to take part in the study. Participation of the study is voluntary, and consent will be implied by completion of a self-administered survey (Appendix 4). Anonymity and confidentiality will be maintained by requesting no identifying data; the survey will have a study number for data collection purposes only. The surveys will be returned to a sealed data collection box. Furthermore, only the researcher and supervisor will have access to the raw data.

Data will be stored securely for six years after completion of the study on a password protected computer and the hardcopies will be stored in a locked cupboard.

The study will be conducted according to the principles of the Declaration of Helsinki (48) and the South African Guidelines for Good Clinical Practice (49).

5.6 Research methodology

5.6.1 Research design

A prospective study is one in which a specific population is followed over time to observe an outcome(50).This is a prospective study as data will be collected at the SASA 2018 Congress.

A contextual study is one which refers to a specific group or population, referred to as a “small scale world” (51). This study is contextual as it will be done among anaesthetists attending the SASA 2018 Congress and the Anaesthetic Foundation Refresher Course.

A descriptive study is one in which phenomena are described, or the relationship between variables is examined; no attempt is made to determine cause-and-effect relationships (50). This study aims to describe the current practise of off-label use of dexmedetomidine in South Africa.

5.6.2 Study population

The study population will consist of anaesthetists attending the SASA 2018 Congress and the Anaesthetic Foundation Refresher Course.

5.6.3 Study sample

Sample size

Surveys will be distributed to the accessible population and the sample size will be determined by the number of returned surveys.

Sampling method

In this study a convenience sampling method will be used. Convenience sampling or availability sampling involves participants who are readily available to the researcher (50). All the anaesthetists attending the SASA 2018 Congress and the Anaesthetic Foundation Refresher Course will be invited to participate.

Inclusion and exclusion criteria

The inclusion criteria for this study are:

- all accessible anaesthetists attending the SASA 2018 Congress and Anaesthetic Foundation Refresher Course
- anaesthetists willing to participate.

The exclusion criterion for this study is nurses and clinical associates attending the SASA 2018 Congress or the Anaesthetic Foundation Refresher Course.

5.6.4 Data collection

Survey development

A survey was chosen as a method for data collection because it can determine what the study population knows, thinks or believes. It is an effective tool to directly question the population concerned and allows data collection from a large group (50).

No existing survey could be identified; therefore, a draft survey was developed by the researcher based on a literature review. The draft survey was reviewed by three senior anaesthesiologists in the Department of Anaesthesiology at the University of the Witwatersrand and changes have been incorporated

The self-administered survey (Appendix 3) consists of two sections.

Section 1 includes the following demographic data:

- gender
- age
- sector
- professional designation
- anaesthetic experience

Section 2 contains questions regarding the use of dexmedetomidine:

- use of dexmedetomidine in anaesthetic practice
- population mostly used for (paediatrics or adults)
- procedures and indications for which dexmedetomidine is used for
- dosages of dexmedetomidine
- anaesthetists understanding of off-label use

Data collection

Permission will be obtained from the Chairman of the SASA Congress as well as the Anaesthetic Foundation Refresher Course to collect data. The researcher will stand at the door of the plenary sessions and hand out the survey to all willing participants. The surveys will be accompanied by an information sheet regarding the study and will be attached to the survey. The participants will be requested to fold the completed survey in half and place in a sealed box. These boxes will be placed at strategic places across the conference venue. All surveys will be numbered to keep track of the data returned. The researcher's contact number will be on the information sheet and the researcher will be available to answer any questions.

Blank surveys will be used to determine response rate; however, these will not be included in the analysis of data. Data from incomplete surveys, however, will still be used.

5.6.5 Data analysis

Data will be entered onto a Microsoft Excel spreadsheet and analysed using descriptive statistics. Categorical variables will be described using frequencies and percentages.

A Microsoft Excel spreadsheet will be used to capture data.

5.7 Significance of the study

Dexmedetomidine is widely researched and in the literature numerous uses have been described, however, the registration is currently limited to ICU sedation and analgesia and awake sedation in an monitored anaesthetic setting, as well as for awake fiberoptic intubation (52). Using medication off-label has implications, not just to the patient, but to the health care professional. Due to the restrictions against advertising and marketing of off-label uses of drugs by pharmaceutical companies, it is not known how dexmedetomidine is used off-label in South Africa. Jansen (1) suggests research is generated through the anaesthetic community, therefore the onus rests on the anaesthetic community to determine the off-label uses of dexmedetomidine.

5.8 Validity and reliability of the study

Validity is defined as the accuracy of an instrument to perform an intended measurement (50). Validity describes the extent to which a true value is being represented by a measurement. A valid study means the conclusions are justified based on the study design (53).

Reliability can be described as the consistency with which a measure is achieved and to which random error occurs (53).

The validity and reliability of this study are maintained by:

- use of the appropriate research design

- content and face validity of the survey being ensured by conducting a literature review and expert review
- completion of a standardised survey by participants
- ensuring anonymity and confidentiality
- when entering the data, 10% of the data will be checked to ensure accuracy and quality of the data entry.

5.9 Potential limitations

Limitations are defined as restrictions or problems that may decrease the application of the findings to the general population (54).

The following are limitations to the study.

- The contextual nature of the study restricts its generalisation to the entire anaesthetic community in South Africa.
- Convenience sampling may not adequately represent the practice of the entire anaesthetic population, but rather the participants present at the congress and foundation.
- The sample size will be determined by the willingness to participate in the study which may result in a small sample size.

5.10 Project outline

5.10.1 Time frame

Activity	July 2017	Nov 2017	Nov 2017	Apr 2018	Oct 2018	Nov 2019	Jun 2019	July 2019	Aug 2019	Oct 2019
Proposal preparation										
Literature review										
Proposal submission										
Ethics approval										
Postgraduate approval										
Data collection										
Data analysis										
Draft article										
Submission										

5.10.2 Budget

Item	Price per page	Number of pages	Copies	Total
Proposal	1	15	10	R 150
Ethics	1	10	25	R 250
Post graduate form	1	2	6	R 12
Complete report	1	100	4	R 400
Grand total				**R 812**

The Wits Department of Anaesthesiology will incur the costs of paper and printing.

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5.12 Appendices

Appendix 1 Permission from SASA Congress chairman

SASA Congress 2018
Cape Town International Convention Centre
Cape Town, South Africa
4 – 8 April 2018
Chairman: Dr Sean Chetty
Congress Management:
Eastern Sun Events
Tel: +27 41 374 5654
Email: sasa2018@easternsun.co.za
Website: www.sasacongress.com

Att: Margarethe Feuth
Email: mvanniekerk02@gmail.com
Cell: 0722454530

7 September 2017

Dear Margarethe

Re: Permission to collect data at the SASA 2018 Congress

On behalf of the 2018 SASA Congress Committee, we hereby approve your request for the distribution of your MMED Survey (for data collection purposes) at the upcoming SASA Congress in April 2018.

Kind regards

Dr Sean Chetty
Congress Chairman

PP

Appendix 2 Permission from the Anaesthetic Foundation Refresher Course organiser

eRni <erni@iafrica.com> Wed, Aug 15, 2018, 8:21 PM

to me, Nevi

Hi Margarethe

Thanks for your request to get your questionnaires handed out at the Foundation.

There is no problem with that.
I can get the chairmen of each session to ask for delegates to fill them in.
You can get them packed in the delegates bags with pleasure.
I see you have already been in contact with Nevi our event organiser, Please contact her about getting the questionnaires to her so they can be included in the bag before the meeting.
I have copied her on this email.

Please send me a copy of your questionnaire.

Thanks for registering for the meeting, that's the usual requirement we make to let you hand out questionnaires.

Kind regards

eRni

Appendix 3 Information sheet

Dear colleague

My name is Margarethe. I am a registrar in the WITS Department of Anaesthesiology. I would like to invite you to participate in my MMED research project titled “Off-label use of dexmedetomidine in anaesthesiology in South Africa”. The study report will be submitted to the Faculty of Health Sciences at the University of the Witwatersrand to fulfil the requirements for my MMED degree.

The study aims to describe how dexmedetomidine is used with specific emphasis on the off-label uses. Government prohibits the advertising and marketing of any drug for an indication other than what it is registered for, therefore due to this law, we currently do not know how dexmedetomidine is used in current practice.

Participation is completely voluntary and consent will be implied by your completion and return of the survey. Information will be kept confidential and anonymous as none of your personal details will be required and only the researcher and supervisor will have access to raw data. There is no penalty for not participating in the study.

Kindly return the survey whether completed or not, by placing it in the designated boxes. The numbering of the surveys is for determining the response rate and for data capturing purposes. Completing the survey should take no longer than 10 minutes.

Please ensure that you understand the above information before completing the survey.

Thank you for taking the time to read this information section. If you have any questions, please do not hesitate to contact me.

Sincerely,

Margarethe Feuth (Researcher 0722454530)

Chairperson of HREC (011 7171234)

Appendix 3 Survey

Off-label use of dexmedetomidine in anaesthesiology in South Africa

Please mark the appropriate section with a X. For certain questions, more than one answer may be applicable.

Section 1 - Demographic information

1.1 Gender	
Male	
Female	
1.2 Age	
25– 35 years	
36 – 45 years	
46 – 55 years	
> 55 years	
1.3 Sector	
Public	
Private	
Public and private	
1.4 Professional designation	
General practitioner	
Diploma anaesthetist	
Registrar	
Specialist anaesthetist	
1.5 Anaesthetic experience	
< 5 years	
5 – 10 years	
> 10 years	

Section 2 – Use of dexmedetomidine

2.1 What is your definition of off-label drug use?

2.2 Have you ever used dexmedetomidine in your anaesthetic practise?

	Public	Private
Yes		
No		

If NO, why not?

Not familiar with the drug	
Previous adverse event/s, please specify:	
Other, please specify:	

If the answer is no to both use in the public and private sector, please do not continue with this survey. Fold and place survey in the sealed boxes provided.

2.3In which population have you used dexmedetomidine before?

	Public	Private
Paediatric (under 12 years of age)		
Adult		

2.4 How often do you use dexmedetomidine?

	Public	Private
Almost every anaesthetic		
At least once daily		
At least weekly		
Occasionally		

2.5 Which route/s have you used to administer dexmedetomidine?

	Public	Private
Intravenous		
Intrathecally		
Buccal		
Nasal		
Subcutaneously		
Intra-articular		
Intramuscular		
Other (please specify):		

2.6 Do you use a loading dose with intravenous dexmedetomidine?

Yes	
No	

2.7 If No, please qualify.

2.8 If yes, what loading dosage do you use?

0.10–.5µg/kg over 10 minutes	
0.5–1µg/kg over 10 minutes	
1– 2µg/kg over 10 minutes	
Other, please specify	

2.9 In general, which dosage do you use for maintenance (eg.µg/kg/hr)

0.2 – 0.7µg/kg/hr	
> 0.7µg/kg/hr	
< 0.2ug/kg/hr	

2.10 For which of the following indications have you used dexmedetomidine?

	Public	Private
Conscious sedation and analgesia in theatre		
Sedation and analgesia in Intensive Care in intubated patients		
Sedation and analgesia in Intensive Care in non-intubated patients		
Part of a general anaesthetic		
To treat postoperative delirium/ emergence delirium		
To decrease spinal shivering		
Adjunct to local anaesthetics in regional anaesthesia		
Adjunct to local anaesthetics in neuroaxial anaesthesia (mixed with local anaesthetic)		
For awake fiberoptic intubation		
Paediatric anaesthesia including as premedication		
Intra-articular injection		
Mixed with local for subcutaneous/ skin infiltration		

Thank you for taking the time to complete this survey.

Section 6: Annexures

6.1 Ethics approval

R14/49 Dr Margarethe Feuth et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M171002

NAME: (Principal Investigator)	Dr Margarethe Feuth et al
DEPARTMENT:	Anaesthesiology 2018 South African Society of Anaesthetists Congress
PROJECT TITLE:	Off-Label use of Dexmedetomidine in Anaesthesiology in South Africa
DATE CONSIDERED:	27/10/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Juan Scribante
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/11/2017

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authoriz to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Margarethe Feuth — Principal Investigator Signature

24 November 2017 — Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

6.2 Postgraduate studies approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

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

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

20 February 2018
Person No: 1537445
PAG

Dr M Feuth
Po Box 6107
Meyersdal
Meyersdal
1447
South Africa

Dear Dr Feuth

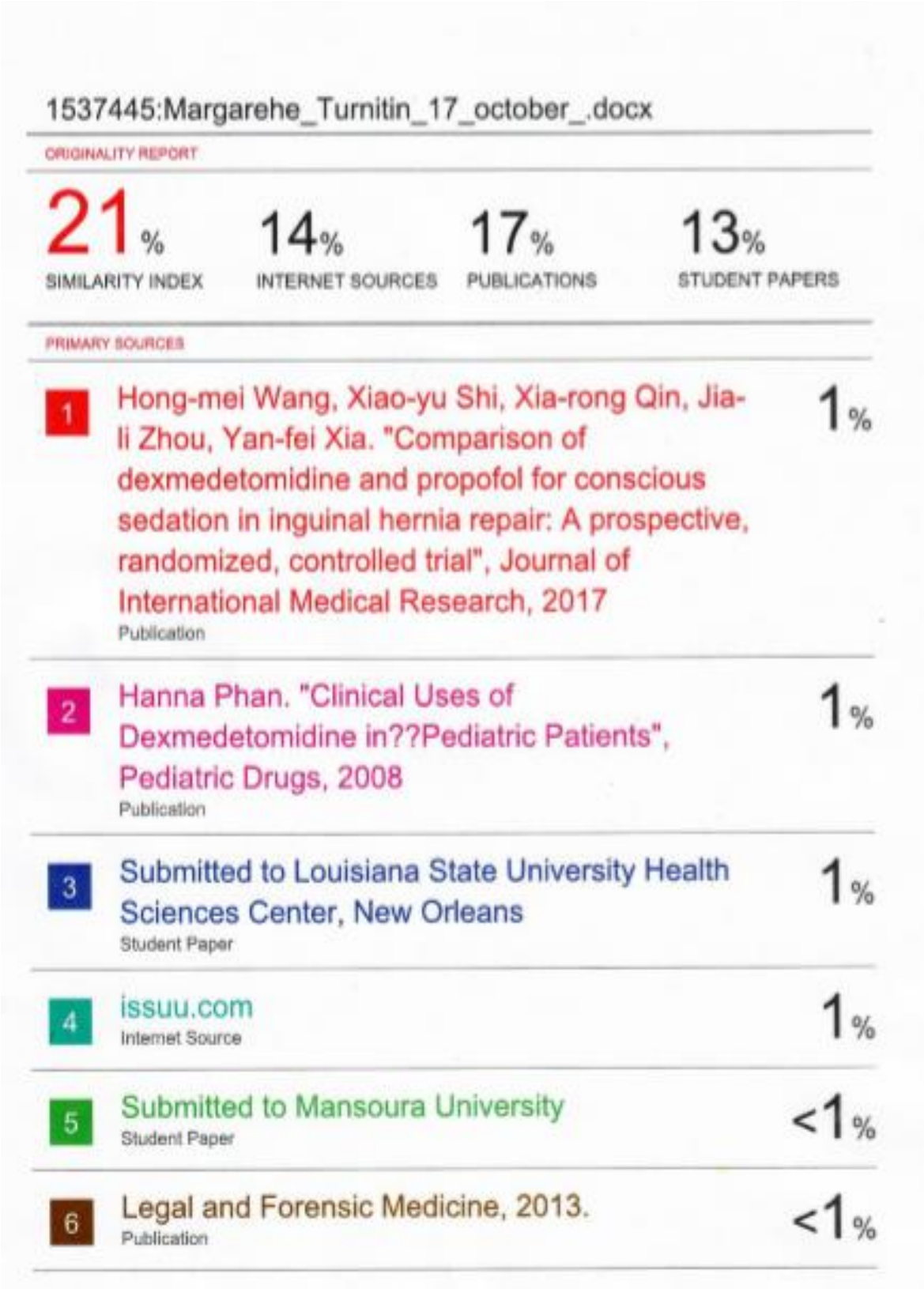
Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Off-label use of Dexmedetomidine in anaesthesiology in South Africa* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

6.3 Turnitin report



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ORIGINALITY REPORT

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1	Hong-mei Wang, Xiao-yu Shi, Xia-rong Qin, Jia-li Zhou, Yan-fei Xia. "Comparison of dexmedetomidine and propofol for conscious sedation in inguinal hernia repair: A prospective, randomized, controlled trial", Journal of International Medical Research, 2017 Publication	1%
2	Hanna Phan. "Clinical Uses of Dexmedetomidine in??Pediatric Patients", Pediatric Drugs, 2008 Publication	1%
3	Submitted to Louisiana State University Health Sciences Center, New Orleans Student Paper	1%
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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

18 October 2019

The Chairperson
Graduate Studies Committee
Faculty of Health Sciences University of the Witwatersrand

Dear Professor Papathanasopoulos

Re: M Med: **Off-label use of Dexmedetomidine in anaesthesiology in South Africa**

Dr Margarethe Feuth, student number: 1537445, has submitted her research report to Turnitin which revealed a similarity index of 21%. These similarities appear not to be plagiarism but mainly the use of common terminology and phrases specific to the topic of the research.

Yours sincerely,

J. Scribante

Juan Scribante
Supervisor