Emergence delirium in children undergoing botulinum toxin injections for strabismus correction

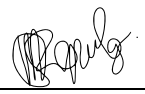
Aletta Rapuleng

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

Johannesburg, 2021

Declaration

I, Aletta Rapuleng 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.



06/12/2021

Abstract

Background

Emergence delirium is an unpleasant complication that may occur in children after general anaesthesia. Botulinum toxin injections for strabismus correction is a short procedure with rapid recovery from anaesthesia, a risk factor for emergence delirium. The aim of this study was to describe the occurrence of emergence delirium and the associated risk factors in children undergoing botulinum toxin injections for strabismus correction at Chris Hani Baragwanath Academic Hospital.

Methods

A cross-sectional research study design was followed using convenience sampling. The study included ASA I and II children aged 2 – 6 years. Data collected consisted of the participants characteristics, the intraoperative course and the child's anxiety level as evaluated at induction using the modified Yale Preoperative Anxiety Scale (mYPAS). The Paediatric Anaesthesia Emergence Delirium (PAED) score was used to diagnose emergence delirium in the recovery room. All children received a standardised anaesthetic.

Results

Sixty-one children were included in the study and 31 (50.8%) developed emergence delirium. Thirty-nine (63.9%) participants showed signs of anxiety with a mean (SD) mYPAS of 41.2 (17.9) out of 100. There was a very weak negative correlation between the highest PAED score and the highest mYPAS (r =-0.0287, p=0.8260). There was a moderate negative, statistically significant correlation between the highest PAED score and age (r =-4850, p=0.0001). Younger age (p=0.0001) and male sex (p=0.0002) were found to predispose participants to emergence delirium. The length of stay in the recovery room was longer in those who experienced emergence.

Conclusion

In this study, a high occurrence of emergence delirium was found following sevoflurane anaesthesia for botulinum toxin injections for strabismus correction, a short procedure with rapid awakening. Younger preschool children were more likely to develop emergence delirium. It was, however, self-limiting and seldom required treatment.

Acknowledgements

The successful completion of this project would not have been possible without the support, advice, assistance and encouragement by others. I extend my sincere gratitude and appreciation to my supervisors Helen Perrie, Juan Scribante and Maria Fourtounas for their tireless guidance and support through this project. I would like to thank the Department of Anaesthesiology and the Department of Ophthalmology at CHBAH for their assistance with my research. To my family and friends, I would not have done this without your support and sacrifices. Thank you for being my number one fans.

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Abbreviations

ASA	American Society of Anesthesiologists
ADVANCE	Anxiety reduction, distraction, video modelling and education, adding parents, no excessive reassurance, coaching and exposure/shaping
CHBAH	Chris Hani Baragwanath Academic Hospital
mYPAS	modified Yale Preoperative Anxiety Score
PAED	Paediatric Anaesthesia Emergence Delirium scale
Wits	University of the Witswatersrand

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 author guidelines of the Southern African Journal of Anaesthesia and Analgesia, the journal to which it is intended to be submitted, in order to comply with the University's style guide.

Section 1: Review of the literature

1.1 Introduction

Strabismus is a condition in which the eyes are not aligned correctly with each other (1). One or both eyes may deviate from the centre and cause loss of depth perception, double or blurred vision (1). Strabismus, commonly known as a squint, develops in childhood and may need to be surgically corrected under general anaesthesia. Alternative treatment modalities for strabismus correction include the use of prisms, orthoptic exercises and injection of botulinum toxin into the eye muscles (1, 2).

Botulinum toxin is produced from the bacteria called *Clostridium botulinum (1).* It causes a reversible short-lived paralysis of the extraocular muscles, with the ability to produce changes in eye position and alignment (2). Botulinum toxin acts by interfering with presynaptic calcium release on the muscle nerve endings, which inhibits the release of acetylcholine and therefore, the muscle fibres do not contract (2). When muscle paralysis occurs, the opposing muscle overrides the paralysed muscle and changes the eye's position and its alignment (2).

The botulinum toxin has a slow and progressive action, it takes effect in about 3 – 5 days after it has been injected. The effect of botulinum toxin wanes after 3 – 6 months, while the alignment of visual axes occurs (1, 2). The correction of strabismus with botulinum toxin is only painful as it is being injected and patients can go home on the day of the procedure (1).

The disadvantage of the effect of botulinum toxin is that it may persist or revert, which means some patients may need repeated injections to correct their strabismus (2). In 2017 Cochrane review on botulinum toxin for the treatment of strabismus (3), found that the use botulinum toxin injections in children needing surgical intervention to correct the strabismus to be of no benefit in achieving the correct alignment of the eyes compared to surgery (3). Nevertheless, the management of strabismus with a botulinum toxin injections has been deemed a better alternative to surgical intervention which involves surgical incision, longer recovery time and a longer hospital stay (1).

1.2 Emergence delirium

Emergence delirium is defined as “a disturbance in a child’s awareness or attention to their environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in the immediate post anaesthesia period” (4). Emergence delirium presents as a dissociated state of consciousness; the child is irritable, uncooperative, crying inconsolably with the head tilting backwards, kicking and thrashing behaviour (4-6). Emergence delirium is also referred to as emergence agitation in the literature (7).

The child may not recognise family members, familiar objects and the environment in which they find themselves (4-6). During this period, the child may pull out intravenous lines and drains or cause disruption of sutures and dressings at the operation site (5). These children display non-purposeful behaviour, they do not react appropriately to external stimuli and they may injure themselves (5). Emergence delirium typically occurs within 5 – 15 minutes of recovery from anaesthesia and it is usually self-limiting; it typically resolves spontaneously within 30 minutes. However, it can last up to two days and the long-term effects are unknown (4).

Some studies suggest that children who experience emergence delirium may display postoperative behavioural problems that were not present prior to anaesthesia (7). These behavioural problems manifest as regression of milestones, separation anxiety, sleep disorders, eating disturbances, aggression and apathy (7).

1.3 Incidence of emergence delirium

The literature reports a high incidence of emergence delirium in children, ranging between 10 – 80% (5, 8). The incidence of emergence delirium depends on the definition employed, age, preoperative anxiety, anaesthetic technique, surgical procedure and administration of adjuvant medication (5). The wide range in the incidence of emergence delirium has been attributed to different study designs, methodology and the measuring scale used (9).

Sethi et al. (10) conducted a study that compared the use of sevoflurane and desflurane to determine the postoperative emergence delirium in children undergoing cataract surgery using the Paediatric Anaesthesia Emergence Delirium (PAED) scale (10). They looked at the paediatric population aged between 2 – 6 years and found an incidence of 18.18% in the sevoflurane group and of 20.45% in the desflurane group, they used a value equal or greater than 12 as having emergence delirium on the PAED scale (10).

Gooden et al. (6) reported an incidence of 19.3% in children aged 3 – 10 years coming for day case surgery following the use of sevoflurane and used the Cravero scale for paediatric emergence delirium (6). The authors found that younger children aged 3 – 6 years had a higher incidence of emergence delirium of 26%, compared to 10% in children aged between 7 – 10 years (6).

1.4 Pathophysiology of emergence delirium

The pathophysiology of emergence delirium is not fully understood and there is insufficient research that focuses on the exact mechanism of how it occurs (4, 5, 11). A multifactorial aetiology is suspected, but there is not enough evidence to validate this (5, 11).

The fast-acting volatile anaesthetic agents such as sevoflurane and desflurane, which cause rapid induction and emergence from anaesthesia, have been associated with emergence delirium (4, 11). The mechanism of action of inhalational anaesthetics may affect brain activity by interfering with the balance between neuronal synaptic excitation and inhibition in the central nervous system (11). The clearance of volatile agents from the central nervous system leads to a differential recovery state of different brain functions (11). Hearing is the first sense to return during emergence from anaesthesia while the recovery of cognitive functions occurs later than other brain functions; this may cause a state of confusion and emergence delirium (11).

1.5 The risk factor

The risk factors for emergence delirium in the paediatric population can be categorised into patient-, anaesthetic- or surgical-related factors (5); and these will be discussed briefly.

Patient-related factors

Emergence delirium occurs predominantly in young preschool children, aged between 2 – 6 years. These children are prone to altered behaviour during recovery from anaesthesia; this may be due to their psychological immaturity and rapid awakening in a strange, unfamiliar environment (5, 12). Furthermore, these children are prone to become agitated and are less able to deal with environmental stressors (5). The younger age group has been associated with a higher risk of preoperative anxiety, a risk factor for emergence delirium (4, 7).

The modified Yale Preoperative Anxiety Scale (mYPAS) is an observational anxiety measuring tool that is used to assess preoperative anxiety in children (13). The mYPAS comprises five items activity, vocalisation, emotional expressivity, state of apparent arousal and use of a parent. It can be applied in the preoperative holding area and during induction of anaesthesia. The child's behaviour is evaluated and a final score varying between 23.33 – 100 is calculated (14). A mYPAS value equal or greater than 30 was found to have a high sensitivity and specificity in predicting preoperative anxiety in children (15). Gooden et al (6) suggested children with a high mYPAS increased the odds of having emergence delirium (6). However, some literature found no correlation between mYPAS and the PAED score (10, 16).

Sex is a risk factor for emergence delirium. Aono et al. (17) suggested that emergence delirium had a greater occurrence in preschool boys aged 3-5 years than school-age boys aged 6-10 years, recovering from sevoflurane anaesthesia. The authors found a higher incidence of 40% in preschool boys and 11.5% in school aged boys after sevoflurane anaesthesia (17). Mohkamkar et al (12), had children aged 3-7 years in their study sample and 134 children had emergence delirium. The authors reported that 11.9% of children who had emergence delirium were males and (6%) of them were females (12).

Parental anxiety also affects the child's preoperative anxiety and can increase the risk of emergence delirium (7). Studies have shown that the child's temperament and preoperative anxiety are risk factors for developing emergence delirium (5, 7, 9, 12). It has been reported that children who are more emotional, more impulsive, less social and less adaptable to environmental changes are at a higher risk for emergence delirium (5, 7, 9).

Anaesthetic factors

An increased risk of emergence delirium is associated with a general anaesthetic using volatile anaesthetic agents that may result in rapid emergence from anaesthesia (4, 7). The rapid awakening can cause the child to wake up confused and disorientated (5, 7). Studies have suggested that the duration of anaesthesia was not a significant factor in the development of emergence delirium, but that rapid awakening from anaesthesia was associated with emergence delirium (18, 19).

The new short-acting volatile agents, namely sevoflurane and desflurane, have been associated with an increased risk of emergence delirium, when compared with the older long-acting volatile agents (9, 11). The low blood solubility characteristic of these inhaled anaesthetic agents promotes rapid induction and awakening, which increases vulnerability to emergence delirium (7, 11).

Sevoflurane is the anaesthetic agent of choice in paediatric patients for smooth, rapid induction and maintenance of anaesthesia. This is due to its physical properties, it is non-pungent and less irritating to the airway and causes less cardiovascular depression (6). Park et al (19) reported that there was no significant difference in the incidence of emergence delirium in children undergoing adenotonsillectomy with sevoflurane alone or a mixture of sevoflurane and nitrous oxide.

Surgical factors

The risk of emergence delirium has been associated with surgical procedures including nonsurgical intervention (4, 5, 9). The surgical procedures that have been associated with a higher risk of emergence delirium are head and neck procedures

(5, 7). Otorhinolaryngological procedures such as tonsillectomy and thyroid surgery and ophthalmological procedures have a higher risk of emergence delirium (9, 12).

According to the literature, postoperative pain has been reported as one of the main confounding factors for emergence delirium (5). Inadequate pain relief may be difficult to differentiate from emergence delirium as they share similar clinical features and behavioural patterns (5, 20). However, postoperative pain does not seem to be an independent risk factor for emergence delirium, as the occurrence of emergence delirium has been reported in non-painful procedures, such as radiological imaging, magnetic resonance imaging and eye examination under anaesthesia (4, 5, 20). It has been recommended that postoperative pain be adequately treated with analgesics to eliminate it as one of the differential diagnoses (7, 9, 20).

2.5 Measuring scales for emergence delirium

Different scales that have been developed to assess the incidence and severity of emergence delirium (5, 9). The three most commonly used observational scales in clinical practice and research to assess emergence delirium in young children are the Paediatric Anaesthesia Emergence Delirium (PAED) scale (21), the Cravero scale (22), and the Watcha scale (23). The PAED scale will be used to assess the occurrence of emergence delirium in this study and will be discussed in more detail.

2.5.1 The Paediatric Anaesthesia Emergence Delirium scale

The PAED scale was developed to measure emergence delirium in children by Sikich and Lerman in 2004 (21). The PAED scale consists of five psychometric items that incorporate cognition and agitation as part of the assessment tools. The PAED scale is a 20 point scale scored from 0 – 4, with reverse scoring where relevant (9, 21). The five items are making eye contact with the caregiver, purposeful actions, awareness of the surroundings, restlessness and if the child is inconsolable (21).

A poor capability of the child to make eye contact with the caregiver and decreased awareness of his/her surroundings indicate disturbances in the child's consciousness, with a decreased ability to focus, or maintain attention; which occur during the emergence delirium (5, 21). Non-purposeful movements in a child may indicate cognitive changes that include impairment of memory and perception, as well as a lack of organisation in thinking patterns (5, 21). The child is restless with inconsolable crying, representing a disturbance in psychomotor behaviour and emotion, which are part of the clinical features of emergence delirium (5, 21). However, these features may also reflect pain which is one of the confounding variables for emergence delirium (5, 21).

Sikich and Lerman (21) reported that a PAED score equal or greater than 10 is the most suitable to describe the presence of emergence delirium (21). It was found to have good sensitivity and specificity for the presence or absence of emergence delirium (21). However, other authors suggest that a PAED score of equal or greater than 12 had a better threshold to describe emergence delirium (10, 12).

The PAED scale is considered as a reliable and valid measuring tool for emergence delirium in children in the recovery room (4, 7, 9, 10, 21). Although the PAED scale is validated as a measuring scale for emergence delirium, it is regarded as cumbersome and difficult to use in clinical practice (9, 23).

The PAED scale has also been reported to have limitations, including the subjective nature of its assessments, inter-observer variability, and a high false positive rate; and some of its behavioural factors overlap with features of a child in pain (7, 21). The PAED scale is shown in Table 1 below.

Table 1: The Paediatric Anaesthesia Emergence Delirium scale (21)

Behaviour	Not at all	Just a little	Quite a bit	Very much	Extremely
Make eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surroundings	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

2.5.2 The Cravero scale

The Cravero scale for emergence delirium consists of five points and is considered a simple tool to use in clinical practice (22). The authors described a low threshold for emergence delirium if level 4 was present, and a high threshold when level 5 was present in a child in the recovery room, for more than three minutes (22).

One of the limitations of the Cravero scale is the fourth item, crying is a nonspecific symptom of emergence delirium as it could be due to other causes such as pain, hunger or parental separation and anxiety and the Cravero scale lacks validity (9, 23). The Cravero scale for paediatric emergence delirium is shown in Table 2.

Table 2: The Cravero scale (22)

Behaviour	Level
Obtunded with no response to stimulation	1
Asleep but responsive to movement or stimulation	2
Awake and responsive	3
Crying (for more than 3 minutes)	4
Thrashing behaviour that requires restraint	5

2.5.3 The Watcha scale

The Watcha scale for emergence delirium consists of four points, which assess the behaviour in the recovery room from asleep, or calm, or crying, or agitated and thrashing around (9, 23). The Watcha scale defines the presence of emergence delirium if a child displays Level 3 or 4 behaviour in the recovery room at any time (9, 23). This scale is considered one of the simpler scales to use in clinical practice with a high sensitivity (9, 23). The Watcha scale is shown in Table 3 below.

Table 3: The Watcha scale (23)

Behaviour	Level
Calm	1
Crying, but can be consoled	2
Crying, but cannot be consoled	3
Agitated and thrashing around	4

3.1 Treatment options for emergence delirium

Emergence delirium is a difficult clinical diagnosis that is made by identifying the risk factors preoperatively and having a high index of suspicion in the recovery room(11). The management of emergence delirium mainly focuses on preventative measures which may decrease the development of this phenomenon and improve the outcome (7, 9).

3.1.1 Preoperative anxiety

Preoperative anxiety is one of the major risk factors for emergence delirium. There are strategies that can be employed to reduce preoperative anxiety for both the child and the parents to mitigate emergence delirium (7, 11). These include parental presence during induction, a quiet induction with decreased sensory stimuli, music therapy, clown doctors, role play, information movies before induction and parent information pamphlets (11).

Kain et al. (24) conducted the study ADVANCE (Anxiety-reduction, distraction, video modelling and education, adding parents, no excessive reassurance, coaching and exposure/shaping) which focused on a behavioural preparation programme for the family together with the child before the surgery (24). The programme involved training parents about the methods that may distract the child while in the waiting area and inside the operating theatre during induction of anaesthesia (11, 24). Although ADVANCE is an expensive intervention, it was found to be efficient in the prevention of preoperative anxiety and thereby decreasing the incidence of emergence delirium (24).

3.1.2 Pharmacological treatment for emergence delirium

The medications that are currently used for treatment of emergence delirium also prevent the development of emergence delirium (4, 7, 9). A variety of different agents can be administered as premedication or during induction of anaesthesia; these include benzodiazepines, fentanyl, propofol, ketamine, dexmedetomidine, clonidine, and magnesium sulphate (4, 7).

Midazolam is a benzodiazepine that is commonly used as an anxiolytic in children. It has been reported to decrease anxiety on induction of anaesthesia with sevoflurane and it was found to make it easier to separate the children from their parents (12, 20). However, some studies reported lengthened emergence from anaesthesia and delay in discharge from the recovery room (12, 20).

Fentanyl is a short acting opioid used for the prevention and treatment of emergence delirium. Pain is a confounding factor and one of the risk factors associated with the development of emergence delirium (9, 11, 25). Adequate intraoperative pain relief has been reported to be important in eliminating pain as a risk factor for emergence delirium and in reduction of the manifestation of emergence delirium (7).

The administration of propofol has been reported to be effective in decreasing the incidence of emergence delirium (12). The administration of propofol 0,5 – 1 mg/kg boluses on emergence from inhalational anaesthesia, has been shown to be an effective preventative measure against the development of emergence delirium.

This results in smooth emergence and the child is calmer in the recovery room (5, 7, 11, 12).

The induction and maintenance of anaesthesia using total intravenous anaesthesia with propofol and remifentanil has been reported to show a decrease in the incidence of emergence delirium, as opposed to sevoflurane and other inhalational anaesthetics (7, 26). The literature reports that total intravenous anaesthesia results in a pleasant emergence from anaesthesia with less postoperative pain (7, 26).

Ketamine has been reported to effectively decrease the manifestation of emergence delirium in children after sevoflurane anaesthesia (27). Ketamine can be given as premedication orally or intravenously. It has been suggested that premedication with ketamine is efficient in decreasing emergence delirium (7, 28).

Dexmedetomidine is a selective α-2 agonist with sedative effects without causing respiratory depression. Dexmedetomidine also has analgesic properties with anaesthetic-sparing effects (8). It can be administered via the intravenous, oral or intranasal route. It has been found to decrease the manifestation of emergence delirium in children after sevoflurane anaesthesia without causing haemodynamic instability (7, 20). Clonidine is an α-2 agonist that has sedative and analgesic properties. It also causes a decrease in sympathetic activity which results in hypotension and bradycardia (8). Intravenous administration of clonidine after induction of anaesthesia has been reported to prevent and decrease the incidence of emergence delirium in children (20).

The literature suggests that magnesium sulphate could have a beneficial effect on reducing the manifestation of emergence delirium after anaesthesia with sevoflurane (29-31). Abdulatif et al. (29) conducted a study assessing the effect of magnesium sulphate on the severity of emergence agitation in children aged 4 – 7 years undergoing adenotonsillectomy using sevoflurane anaesthesia (29).

They found that a loading dose of magnesium sulphate of 30 mg/kg administered intravenously over 10 minutes after induction of anaesthesia with sevoflurane, followed by a continuous infusion of 10 mg/kg/hour reduced the incidence and severity of emergence agitation in children (29).

In a study by Elsharnouby et al. (31), magnesium sulphate was used as an adjuvant in children aged 3 – 9 years undergoing adenotonsillectomy using sevoflurane anaesthesia (31). The authors reported that magnesium sulphate reduced the incidence and severity of emergence delirium and pain, with a limited requirement in sevoflurane concentration (31).

Several studies (29-31) have shown that magnesium sulphate has a valuable role in decreasing the manifestation of emergence delirium in children. However, there is limited information on the management of emergence delirium and further studies need to be done.

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Section 3: Draft article

Emergence delirium in children undergoing botulinum toxin injections for strabismus correction

Aletta Rapuleng, MBChB, DA (SA)

Helen Perrie, MSc

Juan Scribante, PhD

Maria Fourtounas, MBChB, Dip HIV Man (SA), DA (DA), FCA (SA), MMed (Anaes)

Department of Anaesthesiology, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand

Corresponding Author

A. Rapuleng

Department of Anaesthesiology
Chris Hani Baragwanath Academic Hospital
26 Chris Hani Rd
Diepkloof, Soweto
Johannesburg
1860

drrapuleng@yahoo.com

(011) 933 9334

Key words: emergence delirium, strabismus correction, botulinum toxin

Introduction

Emergence delirium is defined as “a disturbance in a child’s awareness or attention to their environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in the immediate post anaesthesia period” (1). The child may not recognise the family members or the environment in which they find themselves or they may cry inconsolably and be agitated with thrashing behaviour (1, 2). Emergence delirium typically occurs within five minutes of recovery from anaesthesia and it is usually self-limiting; resolving spontaneously within 30 minutes. However, it can last up to two days and the long-term effects on children’s development are currently unknown (1).

The incidence of emergence delirium has been reported to be between 10 – 80% (1, 3). One study suggested that it occurs more commonly in preschool children, mainly boys (4). The pathophysiology of emergence delirium is poorly understood with limited research focusing on the exact mechanisms (1, 2). A multifactorial aetiology is suspected, but there is currently insufficient evidence to support this (2, 3).

It is suspected that rapid induction and emergence from anaesthesia with a fast-acting volatile anaesthetic agent such as sevoflurane contribute to the development of emergence delirium (1, 3). The mechanism of action of inhalational anaesthetics may affect brain activity by interfering with the balance between neuronal synaptic excitation and inhibition in the central nervous system (3). It is thought that the clearance of volatile agents from the central nervous system leads to a differential recovery state of different brain functions. The recovery of cognitive functions occurs late in contrast to other brain functions and this may cause a state of confusion and emergence delirium (3).

A number of risk factors for emergence delirium have been identified and can be categorised into patient-, anaesthetic- and surgical-related factors (2). Examples of the patient-related factors are young age, sex, preoperative anxiety and the child’s temperament (2, 5). Anaesthetic-related factors include rapid emergence and the use of volatile anaesthetic agents such as sevoflurane (1, 5). The surgical-related risk

factors include the type of surgery, particularly involving the head and neck, and postoperative pain (5). Postoperative pain is an important confounding factor as its features are similar to emergence delirium in younger children (3). Good intraoperative analgesia is required to eliminate pain as a confounding factor (5, 6).

In a similar demographic population, Jooma et al (7) described an emergence delirium incidence of 51.6% in children presenting for dental surgery in a hospital affiliated to the Department of Anaesthesiology at the University of the Witwatersrand (Wits). To the best of the authors' knowledge, the incidence of emergence delirium in children presenting for a short surgical procedure, such as botulinum toxin injection for strabismus correction under general anaesthesia has not been previously reported. The aim of this study was to describe the occurrence of emergence delirium and the associated risk factors in children undergoing botulinum toxin injections for strabismus correction at Chris Hani Baragwanath Academic Hospital (CHBAH).

Methods

Approval to conduct the study was obtained from the Human Research Ethics Committee (Medical) of Wits with clearance certificate number (M180608) and other relevant authorities. A cross-sectional research design was followed.

The study population consisted of ASA I and II children aged between 2 – 6 years receiving botulinum toxin injections for strabismus correction under general anaesthesia at CHBAH. A consecutive, convenience sampling method was used. The sample size was determined in consultation with a biostatistician. A sample size of 61 participants with 80% power was calculated, using Epi Info™ StatCalc, to estimate the prevalence of emergence delirium to a margin of error of 5% assuming a 50% occurrence of emergence delirium in the population (7). The exclusion criteria for this study were refusal of consent or assent, mental impairment and psychiatric disorders, not receiving a standardised anaesthetic and premedication given.

The data collection sheet (Table I) was compiled following an extensive review of the literature and guided by a similar study (7) with a similar population.

Table I: Data collection sheet

- Section 1: Participants characteristics
  - age
  - sex
  - blood glucose
  - ASA classification
  - history of traumatic medical experience
  - previous anaesthetic
  - previous strabismus procedure.
- Section 2: modified Yale Preoperative Anxiety Scale (mYPAS)
  - activity
  - vocalisations
  - emotional expressivity
  - state of apparent arousal
  - use of parents.
- Section 3: Intraoperative course
  - duration of anaesthesia
  - duration of surgery
  - number of eyes injected
  - dose of botulinum toxin
  - intraoperative medications
  - complications and management thereof.
- Section 4: Postoperative course in the recovery room
  - time of arrival in the recovery room
  - state on arrival in the recovery room (awake/arousable/asleep)
  - Paediatric Anxiety Emergence Delirium (PAED) score
  - non-pharmacological and pharmacological interventions
  - start time of emergence delirium
  - stop time of emergence delirium
  - discharge time from the recovery room.

Assent was obtained from the child's anaesthetist and the study and the mYPAS were explained to them. The primary caregiver, the parent or legal guardian allowed to give consent for the child, was approached and invited to participate in the study in the morning as they arrived in theatre. If they agreed, they were asked to sign informed consent and assent was obtained from children aged six years. Thereafter a study number was assigned. The primary caregiver was allowed to accompany the child to theatre for induction of anaesthesia. Section 1 of the data collection sheet was completed by one author (AR) with the help of the caregiver. Section 2, the mYPAS, was completed by the child's anaesthetist. A child obtaining an mYPAS score of equal to or greater than 30 was regarded as anxious.

As per standard practice at CHBAH, the children presenting for strabismus correction do not receive premedication. All the children received a standardised anaesthetic. Standard monitors were applied: electrocardiogram, non-invasive blood pressure, oxygen saturation. The baseline vital signs were recorded and the child was preoxygenated with 100% oxygen by a mask; gas induction with a mixture of sevoflurane, nitrous oxide and oxygen followed. Nitrous oxide was used because there is no air pipeline in the remote theatre where these procedures are performed. An intravenous line was placed by the anaesthetist and the child was given paracetamol 15 mg/kg intravenously. A finger prick was done to check the blood glucose level. The child breathed spontaneously via a mask for the duration of the procedure. Sevoflurane was discontinued once the procedure was completed. The child was allowed to emerge from anaesthesia and transferred to the recovery room and reunited with the caregiver. The child's anaesthetist documented the intraoperative course in Section 3 of the data collection sheet.

In the recovery room, one author (AR) observed the child for emergence delirium and completed Section 4 of the data collection sheet. In this study, a PAED score of equal to or greater than 10 out of 20 was considered indicative of emergence delirium.

If a child presented with emergence delirium in the recovery room, they received either a pharmacological or non-pharmacological intervention, at the discretion of the child's anaesthetist.

The statistical program STATA version 15 (StataCorp, USA) was used for data analysis in consultation with a biostatistician. Categorical variables were described using frequencies and percentages and continuous variables using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. Demographic variables, procedure-related variables and the patients' state on arrival in the recovery room were compared with the development of emergence delirium using Chi-squared or Fishers Exact tests. Time to discharge from the recovery room was compared to the occurrence of emergence delirium using the Mann-Whitney test. Age and blood glucose were compared between those with and without emergence delirium using independent t-tests. Duration of the anaesthetic was compared to the development of emergence delirium using an independent t-test with a Welch correction for unequal variance. The mYPAS score and age were correlated with the highest PAED score using Spearman's rank correlations. A p-value of <0.05 was considered statistically significant.

Results

A total number of 72 patients presented for correction of strabismus during the study period and were invited to participate in the study. Eleven (15.2%) participants were excluded, 4 with cerebral palsy, 3 with trisomy 21 and 4 participants did not receive the standardised anaesthetic. Sixty-one participants were, therefore, included in the study. The characteristics of the participants are shown in Table II.

Table II: Participants' characteristics

Characteristic	Mean	SD
Age (months)	45.2	17.6
Blood glucose (mmol/L)	4.1	0.5
Duration of surgery (minutes)	3.4	1.1
Anaesthetic time (minutes)	12.2	3.6
Length of stay in the recovery room (minutes)	19.7	5.8
Sex	**Number**	**Percentage**
• Male	23	37.7
• Female	38	62.2
ASA classification		
• I	59	96.7
• II	2	3.2
History of traumatic medical experience	3	4.9
History of previous anaesthetic	30	49.1
History of previous botulinum toxin injection	29	47.5
Botulinum toxin injection to both eyes	61	100

The mean (SD) dose of botulinum toxin injected was 6.3 (1.3) units, with a minimum of 5 units and a maximum of 7.5 units. The mean (SD) dose of paracetamol given intravenously intraoperatively was 230.1 (62.3) mg, with a minimum of 150.0 mg and a maximum of 240.0 mg.

Of the 61 participants, 31 (50.8%) developed emergence delirium following anaesthesia. The PAED scale scores for the 5- ,10-, and 20-minute intervals are shown in Table III. Of the participants who had developed emergence delirium, 2 (6.5%) had not exhibited signs of emergence delirium at 5 minutes but achieved a PAED scale score consistent with emergence delirium at 10 minutes. At 20 minutes, 31 (50.8%) participants had been discharged from the recovery room. At

30 minutes, only 4 (6.5%) participants remained in the recovery room, of which 1 (25%) still had emergence delirium.

Table III: PAED scale scores at the different time intervals

PAED scale sores			
	At 5 minutes (n=61)	**At 10 minutes** (n=61)	**At 20 minutes** (n=31)
Mean	9.3	5.8	5.7
SD	4.6	5.3	3.4
Median	9.0	5.0	6.0
IQR	5.0 – 13.0	0.0 – 10.0	5.0 – 8.8
Min	5	0	0
Max	19	19	11
Number with ED*	29 (47.5%)	20 (32.8%)	4 (12.9%)

*ED emergence delirium

The mean (SD) mYPAS of all the participants was 41.2 (17.9), with a minimum of 23.2 and a maximum of 100. Thirty-nine (63.9%) participants exhibited signs of anxiety. The correlation between the highest PAED score and the mYPAS score is shown in Figure 1. There was a very weak negative (r=–0.0287), not statistically significant (p=0.8260) correlation between the two scores.

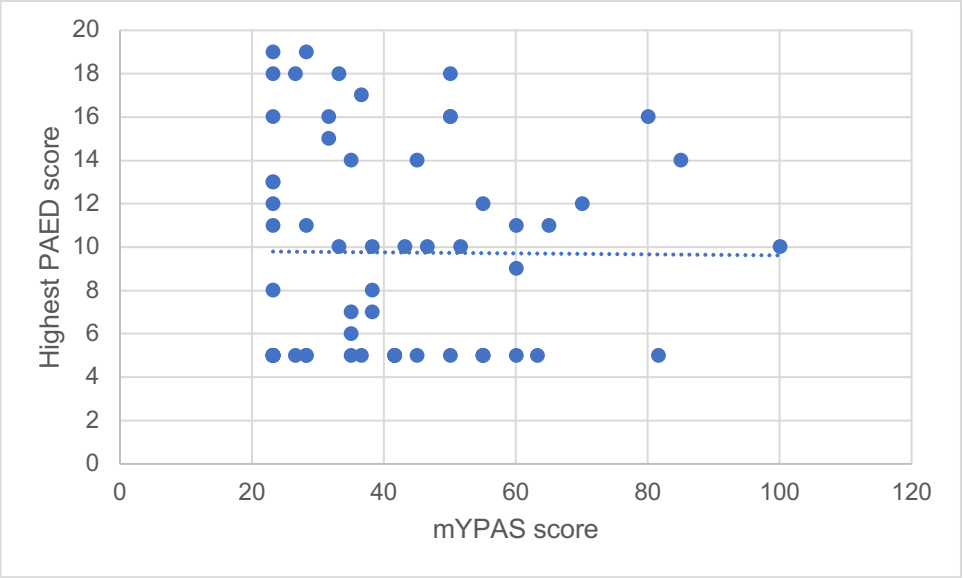

Figure 1: Correlation between the highest mYPAS score and the PAED scores

The correlation between the highest PAED score and age is shown in Figure 2. There was a moderate negative (r=–0.4850), statistically significant (p=0.0001) correlation between the highest PAED scores and age.

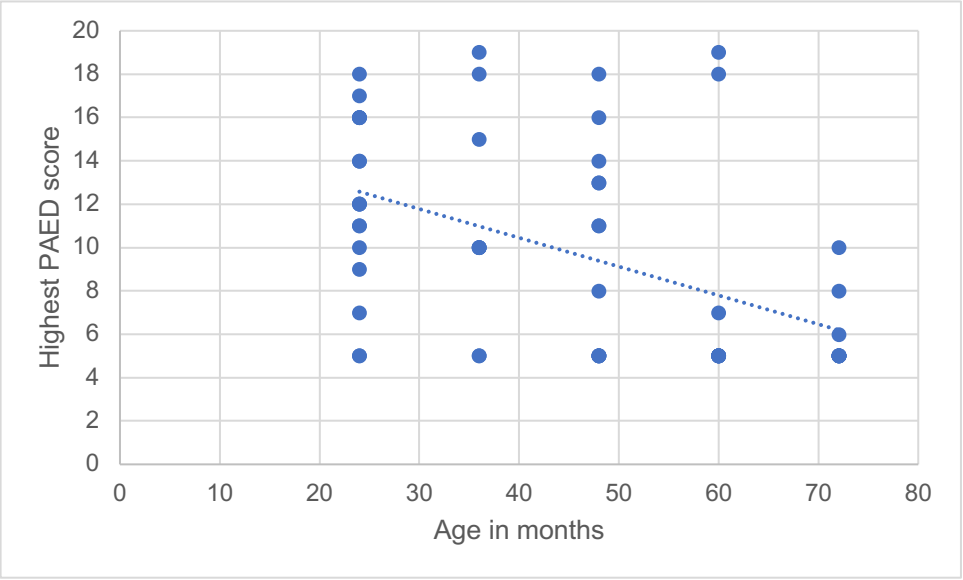

Figure 2: Correlation between the highest PAED score and age

Table IV shows the comparisons between the development of emergence delirium and participant characteristics and procedure-related variables. Three participants were excluded from the glucose analysis as they were given glucose in theatre, none of these 3 participants developed emergence delirium. There were statistically significant differences between the ages and sexes of participants with and without emergence delirium with those developing emergence delirium being younger age and male sex.

Table IV: The comparisons between development of emergence delirium and participant characteristics and procedure-related variables

Variable	Mean (SD)	P-value
Age (months) • ED* • No ED	 36.0 (13.5) 54.8 (16.3)	 0.0001
Blood glucose (mmol/dl) • ED • No ED	 4.2 (0.4) 4.2 (0.5)	 0.9383
Duration of anaesthetic (minutes) • ED • No ED	 13.0 (4.7) 11.3 (1.7)	 0.0778
	Number (%)	
Sex • Male ED / No ED • Female ED / No ED	 19 (31.1) / 4 (6.6) 12 (19.7) / 26 (42.6)	 0.0002
Previous anaesthetic • ED / No ED No previous anaesthetic • ED / No ED	19 (31.1) / 11 (18.0) 12 (19.7) / 19 (31.1)	 0.0744

*ED emergence delirium

On arrival in the recovery room 53 (86.9%) participants were asleep, 4 (6.6%) were arousable and 4 (6.6%) were awake. Of the 31 (50.8%) participants who had

emergence delirium, 28 (90.3%) were consoled by a parent and 3 (9.7%) were consoled by a parent and also received propofol 10 mg intravenously.

The median (IQR) length of stay in the recovery room was 17.0 (15.0 – 24.0) minutes with a range of 13 – 33 minutes. Those with emergence delirium remained in the recovery room for a median (IQR) 24.0 (20.0 – 29.5) minutes and those without emergence delirium remained for 15.0 (15.0 – 16.0) minutes. There was a statistically significant difference between the two with, those with emergence delirium remaining in the recovery room for longer (p=0.0001).

Discussion

Botulinum toxin injections for strabismus correction is a short procedure with rapid emergence from anaesthesia, which has been suspected to predispose a child to emergence delirium (3, 8). Emergence delirium in a child is a disturbing postoperative phenomenon. The child may cry inconsolably and exhibit thrashing behaviour, which may lead to primary caregiver distress and dissatisfaction, staff distress (1), an increased workload and a longer recovery room stay. Mason (5) emphasised the importance of emergence delirium and suggested that it should be considered a vital sign which should be documented for all children in the recovery room.

The incidence of emergence delirium has been reported to be between 10 – 80% for a variety of surgical procedures (1, 3). An occurrence of 50.8% was found in this study. No other studies reporting the incidence of emergence delirium following botulinum toxin injections for strabismus correction could be identified. The incidence found in this study is higher than the 28% reported by Voepel-Lewis et al (8) in other ophthalmic procedures of a different nature and duration. Sethi et al (9) reported an incidence of 18.18% in paediatric patients undergoing cataract surgery with sevoflurane anaesthesia. Jooma et al (7) found an incidence of 51.6%, similar to what was found in our study, in children undergoing dental surgery at the same hospital. It is unlikely that pain influenced the high incidence of emergence delirium found in our study as botulinum toxin injections into the eye are not painful. Furthermore, all participants received paracetamol intravenously during the procedure.

The volatile anaesthetic, sevoflurane, which is an independent risk factor for emergence delirium (2, 3), was used in a mixture with nitrous oxide in this study. Park et al (10) reported that there was no significant difference in the incidence of emergence delirium in children undergoing adenotonsillectomy with sevoflurane alone or a mixture of sevoflurane and nitrous oxide. In this study, nitrous oxide seems not to have influenced the occurrence of emergence delirium as the findings are similar to Jooma et al (7), who used sevoflurane and air.

It has been suggested that the duration of anaesthesia was not a significant factor in the development of emergence delirium, but that rapid awakening from anaesthesia was associated with emergence delirium (8, 10). In this study, the duration of the anaesthetic was found not to be statistically significant between the children who did and did not develop emergence delirium. A gradual washout of sevoflurane and nitrous oxide during emergence from anaesthesia has been shown to decrease emergence delirium (11). A possible explanation for the high incidence of emergence delirium is that the short duration of the anaesthetic may have resulted in a short awakening time, however, measurement of this was beyond the scope of this study.

Emergence delirium usually develops within 5 – 15 minutes but can occur within the first 30 minutes of recovery from anaesthesia (1) and it is usually self-limiting within 14 – 45 minutes (8), with minimal treatment required (2). Of the participants who developed emergence delirium, 29 developed it within five minutes and a further two had developed it by 10 minutes. At 30 minutes, of the four children who remained in the recovery room, only one child was still exhibiting signs of emergence delirium. The majority of our participants were discharged from the recovery room by 20 minutes, which means that those who may have developed emergence delirium later in the course of their recovery could have been missed.

All children in this study who developed emergence delirium were consoled by a parent and only three received propofol 10 mg intravenously to prevent them from thrashing excessively. Other studies suggested that emergence delirium resolved spontaneously without the need for pharmacological intervention (7, 8). None of the participants were restrained to protect them from hurting themselves.

The length of stay in the recovery room in participants who had emergence delirium was significantly longer than those without emergence delirium. Due to the fast turn-over time of the list, all patients with a PAED score of less than 10 were discharged as soon as they were fully awake. Voepel-Lewis et al (8) suggested that the prolonged length of stay in the recovery room resulted from supplemental pharmacological intervention and other supportive treatment. In our study, those who received propofol remained in the recovery room longer.

In this study, it was found that younger age and male sex predisposed participants to emergence delirium. It has been stated that younger children lack the ability to cope with environmental stresses because of the delayed return of cognitive function (3). Other studies also found younger preschool children were more susceptible to develop emergence delirium (6-8). Mohkamkar et al (6) reported, similar to our study, that more males than females developed emergence delirium. This is in contrast to Jooma et al (7) who found no difference in the incidence of emergence delirium between males and females. No explanation has been identified in the literature regarding males being more predisposed to emergence delirium than females.

Preoperative anxiety has been mentioned as a risk factor for emergence delirium (1, 5). In this study, 63.9% of participants showed signs of anxiety and no correlation between anxiety and the development of emergence delirium was found. Regarding this, there are conflicting results in the literature. Gooden et al (4) suggest that high anxiety in a child makes them susceptible to the development of emergence delirium while other authors have reported a negative correlation between anxiety and emergence delirium (7, 9).

The contextual nature of this study and the specific procedure are potential limitations and therefore, the results may not be generalisable to other contexts or surgical procedures. Botulinum toxin injections for strabismus correction is a short procedure with rapid awakening and a fast turn-over of patients in the recovery room. This may have led to some children who developed emergence delirium later in the postoperative period being missed. Further studies that focus on the awakening time from sevoflurane anaesthesia and emergence delirium need to be

conducted as the literature suggests rapid awakening predisposes a child to emergence delirium.

Conclusion

In this study, a high occurrence of emergence delirium was found following sevoflurane and nitrous oxide anaesthesia for botulinum toxin injections for strabismus correction, a short procedure with rapid awakening. Younger preschool children were more likely to develop emergence delirium. It was, however, self-limiting and seldom required treatment. Emergence delirium should be regarded as a vital sign as suggested by Mason (5) and anaesthetists need to recognise, document and manage it appropriately.

Conflict of interest

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

Acknowledgement

This research was done in partial fulfilment of a Master of Medicine degree.

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Section 4: Proposal

Emergence delirium in children undergoing botulinum toxin injections for strabismus correction

Aletta Rapuleng

1823395

Supervisor	Helen Perrie Department of Anaesthesiology
Co-supervisor	Juan Scribante Department of Anaesthesiology
Co-supervisor	Maria Fourtounas Department of Anaesthesiology

4.1 Introduction and problem statement

Young children may present with strabismus and may require a general anaesthetic for corrective surgery. According to Teo and Chee (1) strabismus is a condition in which the eyes are not aligned correctly with each other and one or both eyes may deviate from the centre and cause loss of depth perception, double or blurred vision. The authors further state that one of the methods employed for strabismus correction is the injection of botulinum toxin into the eye muscles (1).

Emergence delirium is defined as “a disturbance in a child’s awareness or attention to their environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in the immediate post anaesthesia period” (2). The child may not recognise the family members, or the environment in which they find themselves, or they may cry inconsolably and be agitated with thrashing behaviour (2, 3). Emergence delirium typically occurs within five minutes of recovery from anaesthesia and it is usually self-limiting; resolving spontaneously within 30 minutes. However, it can last up to two days and the long-term effects on children’s development are currently unknown (2).

The incidence of emergence delirium has been reported to be between 10 – 80% (2, 4). One study suggested that it occurs more commonly in younger preschool children, mainly boys (5). The pathophysiology of emergence delirium is poorly understood with limited research focusing on the exact mechanisms (2, 3). A multifactorial aetiology is suspected, but there is currently insufficient evidence to validate this (3, 4).

It is suspected that rapid induction and emergence from anaesthesia with a fast-acting volatile anaesthetic agent such as sevoflurane contribute to the development of emergence delirium (2, 4). The mechanism of action of inhalational anaesthetics may affect brain activity by interfering with the balance between neuronal synaptic excitation and inhibition in the central nervous system (4). It is thought that the clearance of volatile agents from the central nervous system leads to a differential recovery state of different brain functions; the recovery of cognitive functions occurs late in contrast to other brain functions and this may cause a state of confusion and emergence delirium (4).

A number of risk factors for emergence delirium have been identified and can be categorised into patient-, anaesthetic- and surgical-related factors (3). Examples of the patient-related factors are young age, sex, preoperative anxiety and the child's temperament (3, 6). Anaesthetic-related factors are rapid emergence and the use of volatile anaesthetic agents such as sevoflurane (2, 6). The surgical-related risk factors include the type of surgery, particularly involving the head and neck and postoperative pain (6). Postoperative pain is one of the important confounding factors as it shares the features and presentation with emergence delirium in younger children (4). Good intraoperative analgesia is required to eliminate pain as one of the confounding factors (6, 7).

Several measuring scales have been developed to assess the incidence and the severity of emergence delirium (3, 8). The three most commonly used scales in clinical practice and research are the Paediatric Anaesthesia Emergence Delirium scale (PAED) (9), the Cravero scale (10) and the Watcha scale (11). The PAED scale has a good sensitivity and specificity for the presence or absence of emergence delirium. It is a 20-point scale that consists of five items. A score equal to or greater than 10 has a high likelihood for the diagnosis of emergence delirium (9).

Preoperative anxiety is a risk factor for emergence delirium and it can be measured using the modified Yale Preoperative Anxiety Scale (mYPAS) (12). The preventative measures for emergence delirium mainly focus on reducing preoperative anxiety and these may either be non-pharmacological or pharmacological. The non-pharmacological measures include parental presence on induction of anaesthesia, minimal stimulation on emergence from anaesthesia and allowing the caregiver to console the child in the recovery room (4, 6). The pharmacological measures include the administration of agents such as propofol, fentanyl, clonidine, dexmedetomidine and magnesium sulphate (6).

In a similar demographic population, Jooma (13) described an emergence delirium incidence of 51.6% in children presenting for dental surgery in a hospital affiliated to the Department of Anaesthesiology at the University of the Witwatersrand (Wits). To the best of the researcher's knowledge, the incidence of emergence delirium in children presenting for a short surgical procedure, such as botulinum

toxin injection for strabismus correction under general anaesthesia has not been previously reported. Therefore a study addressing this will be undertaken at Chris Hani Baragwanath Academic Hospital (CHBAH).

4.2 Aim and objectives

4.2.1 Aim

The aim of this study is to describe the occurrence of emergence delirium and the associated risk factors in children undergoing botulinum toxin injections for strabismus correction at CHBAH.

4.2.2 Objectives

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

- describe the occurrence of emergence delirium using the PAED scale
- determine the preoperative anxiety (at induction) using the mYPAS scale
- correlate the development of emergence delirium with anxiety score and age
- compare demographic and procedure-related variables with the development of emergence delirium
- describe the state of arrival in the recovery room with the development of emergence delirium
- describe the management of emergence delirium
- compare the time to discharge from the recovery room of children with and without emergence delirium
- describe the botulinum toxin dose injected and the medication given in the intraoperative period.

4.3 Research assumptions

The following definitions will be used in this study.

Child: in this study, a child will be between 2 – 6 years of age.

Primary caregiver: is the parent or legal guardian allowed to give consent for the child.

PAED scale: is a validated scale developed by Sikich and Lerman (9) to assess emergence delirium in recovery room. (Appendix 1a).

Emergence delirium: in this study, a PAED score of equal or greater than 10 will be considered as emergence delirium.

State of arrival in recovery room: in this study, the child's state of arrival in the recovery room will be described as awake, or arousable or asleep.

mYPAS: an mYPAS is a validated score of equal or greater than 30 will be regarded as anxious. (Appendix 1b).

4.4 Demarcation of study field

CHBAH is a central hospital affiliated to the University of the Witwatersrand. The hospital has 2 888 beds, 25 theatres and performs approximately 65 000 surgeries per annum. On average, 200 strabismus correction procedures are done per annum using botulinum toxin injection.

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 will be obtained from the Medical Advisory Committee at CHBAH (Appendix 2a). Further approval was obtained from the Head of the Department of Anaesthesiology at CHBAH (Appendix 2b).

The researcher will approach the primary caregiver of the child, explain the study to them and then invite the participation of their child. If they agree, the researcher will give them an information letter (Appendix 3a) and ask them to sign a consent form (Appendix 3b). Assent will be obtained from the anaesthetist in charge of the list.

The children's names, hospital numbers and study number will be recorded on a list and filed separately. Data will be collected without identifying information and

will be assigned a study number. Confidentiality will be maintained as only the researcher and the supervisors will have access to the raw data.

If a child presents in the recovery room with emergence delirium, the researcher will notify the anaesthetist who administered anaesthesia to the child and the anaesthetist will give the child appropriate treatment for emergence delirium. The management of emergence delirium will be recorded by the researcher. A child who shows extreme anxiety will be referred to the Department of Psychology at CHBAH for support at the convenience of the caregiver during the available consultation hours.

All data collected will be kept and stored securely on a password protected electronic database and all the data collection sheets will be stored in a locked cupboard for six years after completion of the study.

This study will be conducted according to the principles of the Declaration of Helsinki (14) and the South African Guidelines for Good Clinical Practice (15).

4.5 Research methodology

4.5.1 Research design

A cross-sectional research design will be followed in this study.

Cross-sectional studies are used to examine data at one point in time, the data are collected on only one occasion with different participants (16). Emergence delirium will be described in children presenting for botulinum toxin injections for strabismus correction under general anaesthesia at CHBAH.

4.5.2 Study population

The study population consists of children aged between 2 – 6 years receiving botulinum toxin injections for strabismus correction under general anaesthesia at CHBAH.

4.5.3 Study sample

Sample size

The sample size was determined in consultation with a biostatistician. A sample size of 61 participants was calculated, using Epi Info™ StatCalc, to estimate the prevalence of emergence delirium to a margin of error of 5% assuming a 50% occurrence of emergence delirium in the population (13).This sample size can achieve a minimum power of 80% on hypothesis testing.

Sampling method

A consecutive, convenience sampling method will be used in this study. Convenience sampling involves participants who are readily available to the researcher (16). According to Endacott (17), consecutive sampling is “a version of convenience sampling where every available individual or event within an accessible population is chosen” (17).

In this study consecutive, convenience sampling means that on the day of the procedure every primary caregiver of the children presenting for botulinum toxin injections for strabismus correction will be approached and invited to take part in the study, provided they meet the inclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria for this study are:

- ASA I and II
- aged 2 – 6 years
- receiving botulinum toxin injections for strabismus correction.

The exclusion criteria in this study are:

- refusal of consent or assent
- mental retardation
- not receiving a standardised anaesthetic
- premedication given

- children with psychiatric disorders.

4.5.4 Data collection

Data collection sheet

The data collection sheet (Appendix 4) was compiled following an extensive review of the literature and guided by a similar study (13) and population at the University of the Witwatersrand.
The data collection sheet consists of four sections.

- Section 1 consists of the following demographics:
    - age
    - sex
    - blood glucose
    - ASA classification
    - history of traumatic medical experience
    - previous anaesthetic
    - previous strabismus procedure.
- Section 2 consists of the mYPAS measuring the child's preoperative level of anxiety:
    - activity
    - vocalisations
    - emotional expressivity
    - state of apparent arousal
    - use of parents.
- Section 3 documents the intraoperative course
    - duration of anaesthesia
    - duration of surgery
    - number of eyes injected
    - dose of botulinum toxin
    - intraoperative medications
    - complications and management thereof.
- Section 4 documents the postoperative course in the recovery room:
    - time of arrival in recovery room
    - state on arrival in recovery room (awake/arousable/asleep)

- PAED score
- non-pharmacological and pharmacological interventions
- start time of emergence delirium
- stop time of emergence delirium
- discharge time from the recovery room.

Data collection

The primary caregiver will be approached and invited to participate in the study in the morning as they arrive in theatre. The study will be explained to them and they will be given an information letter (Appendix 3a). If they agree, they will be asked to sign informed consent (Appendix 3b). Assent (Appendix 3c) will be obtained from children aged six years. Thereafter a study number will be assigned. The primary caregiver will be allowed to accompany their child to theatre for induction of anaesthesia. Assent will be obtained from the anaesthetist in charge of the list.

Section 1 of the data collection sheet will be completed by the researcher with the help of the caregiver. Section 2, the mYPAS, will be completed by the anaesthetist allocated to the list, who will have had the study and the mYPAS explained to them before induction of anaesthesia in theatre.

As per standard practice on this list at CHBAH the children will not receive premedication. The anaesthetist allocated to the list will be given a standardised anaesthetic protocol (Appendix 5) and all the children will receive a standardised anaesthetic. Standard monitors will be applied: electrocardiogram, non-invasive blood pressure, oxygen saturation. The baseline vitals will be recorded and the child will be preoxygenated with 100% oxygen by a mask; gas induction with a mixture of sevoflurane, nitrous oxide and oxygen. Nitrous oxide will be used because there is no air pipeline in the theatre where these procedures are done. An intravenous line will be placed and the child will be given paracetamol 15 mg/kg intravenously, or a per rectal paracetamol dose of 40mg/kg will be given to the child, with prior consent from the caregiver, by the anaesthetist. A finger prick will be done to check the blood glucose level. The child will breathe spontaneously via a mask and the mask will not be removed from the airway for the duration of

the procedure. The surgeon will commence the procedure. Sevoflurane will be discontinued once the procedure is done. The child will be allowed to emerge from anaesthesia and transferred to the recovery room, where they will be reunited with the caregiver.

In the recovery room, the researcher will observe the child for emergence delirium and complete Section 4 of the data collection sheet. In this study, a PAED score of equal or greater than 10 will be considered as having emergence delirium.

If a child presents with emergence delirium in the recovery room they will receive either a pharmacological or non-pharmacological intervention, this will be at the discretion of the anaesthetist in charge of the list for the day and this will be recorded on the data collection sheet. A child with extreme anxiety, according to the mYPAS, will be referred to the Department of Psychology at CHBAH for support after the procedure is done and at the convenience of the caregiver during the available consultation hours.

4.5.5 Data analysis

Data will be captured onto a Microsoft Excel® spreadsheet. Data analysis will be done in consultation with a biostatistician. The statistical program STATA version 15 (StataCorp, USA) will be used. Categorical variables will be described using frequencies and percentages and continuous variables using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. Demographic variables and procedure-related variables will be compared with the development of emergence delirium using Chi-squared or Fishers Exact tests. The mYPAS score and age will be correlated with the highest PAED score using Pearson's or Spearman's rank correlations. The patients state on arrival in the recovery room will be compared to the occurrence of emergence delirium using either Chi-squared or Fishers Exact test. Time to discharge from the recovery room will be compared to the occurrence of emergence delirium using either the Students t-test or the Mann-Whitney test depending on whether the data are normally distributed or not. A p-value of <0.05 will be considered statistically significant.

4.6 Significance of the study

Emergence delirium in a child is a disturbing postoperative phenomenon. The child may cry inconsolably and exhibit thrashing behaviour which may lead to primary caregiver distress and dissatisfaction (2), staff distress and an increased workload. Furthermore, the recovery room stay may be lengthened. Young age has been identified as one of the risk factors of preoperative anxiety (2, 6). Preschool children who are less able to deal with environmental stressors and are prone to develop emergence delirium frequently present for strabismus correction under general anaesthetic (3). The long-term impact of emergence delirium on a child is currently unknown (2).

Botulinum toxin injections for strabismus correction is a short procedure with a fast turnover between patients. Sevoflurane is the volatile anaesthetic agent of choice in children for smooth rapid induction and emergence from anaesthesia, but it has been suggested to be one of the risk factors for emergence delirium (3, 6).

The occurrence of emergence delirium in children receiving botulinum toxin injections for strabismus repair is not known at CHBAH. This study will describe the occurrence of emergence delirium in this population group. If the occurrence is high, it may be possible to put pharmacological and non-pharmacological measures in place to reduce and prevent emergence delirium.

4.7 Validity and reliability of the study

Validity refers to the degree to which a measurement represents a true value and reliability represents the consistency of the measure achieved (18).

The validity and reliability of this study will be ensured by:

- using an appropriate study design
- sample size determined in consultation with a biostatistician
- non-painful procedure, therefore, emergence delirium should not be confused with pain
- children will receive a standardised anaesthetic

- using validated scoring systems:
    - mYPAS scale to assess anxiety
    - PAED scale to assess emergence delirium
- a single researcher scoring the PAED scale
- checking every tenth data entry for accuracy
- data analysis will be done with the assistance of a biostatistician.

4.8 Potential limitations

Limitations are defined as restrictions or problems that may decrease the application of the findings to the general population (19).

A potential limitation of this study is that it is difficult to determine the causal relationship from a cross-sectional analysis. Another potential limitation of this study is that it has a contextual design. The results may therefore not be generalisable to other surgical procedures or other contexts, however it will provide valuable information on emergence delirium in children presenting at CHBAH.

4.9 Project outline

4.9.1 Time frame

Activity	Oct 2018	Mar 2019	Jun 2019	Aug 2019	Sep 2019	Jan 2020	Mar 2020	Apr 2020	Aug 2020	Sep 2020	Oct 2020
Proposal											
Proposal submission											
Ethics approval											
Graduate studies approval											
Data collection											
Data analysis											
Article preparation											
Submission											

4.9.2 Budget

The Department of Anaesthesiology will bear the cost of printing and paper for the proposal, ethics and post graduate applications.

Item	Price per page	No of pages	Copies needed	Total
Proposal	R 1	20	10	R 200
Ethics Application form	R 1	10	25	R 250
Post graduate application form	R 1	1	6	R 6
Completed research report	R 1	100	4	R 400
Binding	R 150		3	R 450
Grand total				R 1306

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4.11 Appendices

Appendix 1a: the Paediatric Anaesthesia Emergence Delirium scale (PAED)

Behaviour	Not at all	Just a little	Quite a bit	Very much	Extremely
Make eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surroundings	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

Appendix 1b

Section 2: The modified Yale Preoperative Anxiety Scale

Activity

1	Looks around, curious, plays with toys, reads (or other age-appropriate behaviour); moves around to get toys or go to parent; may move toward theatre or surgery equipment
2	Not exploring or playing, may look down, fidgets with hands or suck thumb or blanket; may sit close to parent while waiting, or play has a manic quality
3	Moving from toy to parent in unfocused manner, non-activity derived movements; frantic movement or play; squirming, moving on table, may push mask away, or clings to parent
4	Actively tries to get away, pushes with feet and arms, may move whole body; in waiting room, running around unfocused, not looking at toys or desperate clinging to parent

Vocalisation

1	Reads (non-vocalising appropriate to activity), asks questions, makes comments, babbling, laughing, readily answers questions but may be generally quiet; child too young to talk in social situations or too engrossed in play to respond
2	Responding to adults but whispers, “baby talk,” only head nodding
3	Quiet, no sounds or responses to adults
4	Whimpering, moaning, groaning, silently crying
5	Crying or may be screaming “no”
6	Crying, screaming loudly, sustained (audible through mask)

Emotional expressivity

1	Manifestly happy, smiling, or concentrating on play
2	Neutral, no visible expression on face
3	Worried, frightened, sad; worried or tearful eyes
4	Distressed, crying, extremely upset, may have wide eyes

State of apparent arousal

1	Alert, looks around occasionally, notices or watches what anaesthetist does with him/her (could be relaxed)
2	Withdrawn, child sitting still and quiet, may be sucking on thumb or face turned into adult
3	Vigilant, looking quickly all around, may startle to sounds, eyes wide, body tensed
4	Panicked whimpering, may be crying or pushing others away, turns away

Use of parents

1	Playing, sitting idle, or engaged in age appropriate behaviour and does not need parent; may interact with parent if parent initiates the interaction
2	Reaches out to parent (approaches and speaks to otherwise silent parent), seeks and accepts comfort, may lean against parent
3	Looks to parents quietly, watches actions, does not seek contact or comfort, and accepts it if offered or clings to parent
4	Keeps parent at distance or may actively withdraw from parent, may push parent away or desperately clinging to parent and will not let go

Total = /4 + /6+ /4+ /4 + /4= $\times 20 =$

Appendix 2a: Request to the Medical Advisory Committee of Chris Hani Baragwanath Academic Hospital

Title: Emergence delirium in children undergoing botulinum toxin injections for strabismus correction

Dr Aletta Rapuleng

Department of Anaesthesiology

University of the Witwatersrand

Dear Sir or Madam

I am a registrar in the Department of Anaesthesiology. I am currently doing my research for the Master of Medicine in Anaesthesiology. My research involves describing emergence delirium in paediatric patients receiving botulinum toxin injections for strabismus correction at CHBAH.

The study has been approved by the Human Research Ethics Committee (ethical clearance number) and the Graduates Studies Committee of the University of the Witwatersrand.

I would like to request permission to investigate the objectives of the research. There will be no added cost to the hospital as a result of the study. The report of the study will be made available to you.

Kind regards

Dr Aletta Rapuleng

0722113064

drrapuleng@yahoo.com

Appendix 3a: Information letter (Parent(s)/Guardian)

Title: Emergence delirium in children undergoing botulinum toxin injections for strabismus correction

Dear Parent(s)/Guardian

Hello, my name is Dr Aletta Rapuleng. I am studying to become an anaesthetist at the University of the Witwatersrand. An anaesthetist is a doctor who make patients sleep for an operation and takes care of patients while they are in theatre. We ensure that patients do not remember or feel anything during the operation and we give medication to take away the pain after the operation.

I need to do research as part of my studies and I would like to invite your child to take part. Children may wake up from the anaesthetic confused, crying, kicking and screaming; this is called emergence delirium. This happens because of the medication we use to make them sleep during the operation. If this happens, they will not remember it and it only lasts for a short while. The researcher will notify the child's attending anaesthetist, who will give the child appropriate treatment of emergence delirium and the researcher will record the management of emergence delirium. I would like to find out how many children have emergence delirium when they wake up from anaesthesia.

Taking part in this study is completely voluntary and if you agree I will ask you to sign a consent form and if your child is six years old I will ask them if they are willing to take part as well and ask them to sign an assent form. I will ask you a few questions about your child and this will take less than five minutes. You will accompany your child to theatre until they fall asleep, then you will wait for them outside and be reunited when they return to the recovery room.

Your child will receive normal anaesthetic and pain medication. You are welcome to ask more questions with regards to the study and what it entails, I will happily answer all your questions. Please note confidentiality will be maintained and your child's information will remain anonymous.

Your child being part of the study will help us understand emergence delirium and children's behaviour in theatre better. It may also help us plan a better anaesthetic for children to decrease emergence delirium.

If you do not want your child to take part in the study or you withdraw at any point, your child will still receive normal anaesthetic as other children but will not be included in the study. The doctors and nurses will not be upset with you or child.

Signing your name on the consent form means that you agree that your child will participate. You will be given a copy of this form to keep.

This study has been approved by the Human Research Ethics Committee (Medical) (011 717-1234) and the Graduates Studies Committee of the University of the Witwatersrand.

Kind regards

Aletta Rapuleng.

Tel.011 933

drrapuleng@yahoo.com

HREC (Medical) Chairperson: Dr Clement Penny

Clement.Penny@wits.ac.za

Or

Administration Officer: Human Research Ethics Committee (Medical)

Tel. 011 717-1234/2656/2700

Zanele.Ndlovu@wits.ac.za / Rhulani.Mkansi@wits.ac.za / Charmaine.Khumalo@wits.ac.za / Josh.Ndlangamandla@wits.ac.za

Thank you for taking the time to read this information letter and for your child's participation.

Appendix 3b: CONSENT TO PARTICIPATE IN RESEARCH STUDY

Title: Emergence delirium in children undergoing botulinum toxin injections for strabismus correction

I _____, parent/ legal guardian of _____ give consent for my child/the child I care for to participate in this study. I understand what this study is about, I have read and understand the information letter and my questions have been answered. I am aware that I may withdraw my child from the study at any time without any prejudice toward the child or me. I understand that my name and that of my child will not appear in any of the results of the research.

Print Name of Parent or Guardian:

_____

Signature of Parent or Guardian:

_____

Date: _____

Name of researcher:

_____

Signature of researcher:

_____

Date: _____

Appendix 3c: Assent to participate

ASSENT TO PARTICIPATE IN RESEARCH STUDY

Title: Emergence delirium in children undergoing botulinum toxin injections for strabismus correction

I _____, agree to participate in this study. I understand what the study is about and my questions have been answered. I know that I can say that I don't want to be part of this study at any time. I know that nobody will see my name and know that I was part of the study when it is finished.

Name of participant:

_____

Signature of participant:

_____

Date: _____

Name of researcher:

_____

Signature of researcher:

_____

Date:

_____

Appendix 4: Data collection sheet

Section 1:

Date	

Study number	

Section 1: Personal details

Age (months)		
Blood glucose		
Sex	M	F
ASA classification	I	II
History of traumatic medical experience	Yes	No
Previous anaesthetic	Yes	No
Previous botulinum toxin injection	Yes	No

Section 2: The modified Yale Preoperative Anxiety Scale

Activity

1	Looks around, curious, plays with toys, reads (or other age-appropriate behaviour); moves around to get toys or go to parent; may move toward theatre or surgery equipment
2	Not exploring or playing, may look down, fidgets with hands or suck thumb or blanket; may sit close to parent while waiting, or play has a manic quality
3	Moving from toy to parent in unfocused manner, non-activity derived movements; frantic movement or play; squirming, moving on table, may push mask away, or clings to parent
4	Actively tries to get away, pushes with feet and arms, may move whole body; in waiting room, running around unfocused, not looking at toys or desperate clinging to parent

Vocalisation

1	Reads (non-vocalising appropriate to activity), asks questions, makes comments, babbling, laughing, readily answers questions but may be generally quiet; child too young to talk in social situations or too engrossed in play to respond
2	Responding to adults but whispers, “baby talk,” only head nodding
3	Quiet, no sounds or responses to adults
4	Whimpering, moaning, groaning, silently crying
5	Crying or may be screaming “no”
6	Crying, screaming loudly, sustained (audible through mask)

Emotional expressivity

1	Manifestly happy, smiling, or concentrating on play
2	Neutral, no visible expression on face
3	Worried, frightened, sad; worried or tearful eyes
4	Distressed, crying, extremely upset, may have wide eyes

State of apparent arousal

1	Alert, looks around occasionally, notices or watches what anaesthetist does with him/her (could be relaxed)
2	Withdrawn, child sitting still and quiet, may be sucking on thumb or face turned into adult
3	Vigilant, looking quickly all around, may startle to sounds, eyes wide, body tensed
4	Panicked whimpering, may be crying or pushing others away, turns away

Use of parents

1	Playing, sitting idle, or engaged in age appropriate behaviour and does not need parent; may interact with parent if parent initiates the interaction
2	Reaches out to parent (approaches and speaks to otherwise silent parent), seeks and accepts comfort, may lean against parent
3	Looks to parents quietly, watches actions, does not seek contact or comfort, and accepts it if offered or clings to parent
4	Keeps parent at distance or may actively withdraw from parent, may push parent away or desperately clinging to parent and will not let go

Total = /4 + /6+ /4+ /4 + /4= $\times 20 =$

Section 3: Intraoperative course

Anaesthesiology	Start time	
	End time	
Surgery	Start time	
	End time	

Number of eyes injected	
Botulinum toxin dose	

Intraoperative medication (dose)	Paracetamol	
	Anti-emetic	
	Other (specify)	
	Other (specify)	

Complications	Laryngospasm	
	Bronchospasm	
	Allergic reaction	
	Other (specify)	
	None	

Management of complications

Section 4: Postoperative course

Time of arrival in recovery room	

State on arrival in recovery room	Awake	
	Arousable	
	Asleep	

PAED score						
Point	**Description**	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Extremely**
1	The child makes contact with the caregiver	4	3	2	1	0
2	The child's actions are purposeful	4	3	2	1	0
3	The child is aware of his/her surroundings	4	3	2	1	0
4	The child is restless	0	1	2	3	4
5	The child is inconsolable	0	1	2	3	4

Paeds score at:	5 minutes	
	10 minutes	
	20 minutes	
	30 minutes	

ED	Start time	
	End time	

Management of ED	None	
	Physical restraints	
	Consoled by parent	
	Medication (specify)	

Time of discharge from recovery	

Section 5: Annexures

5.1 Ethics approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr MA Rapuleng, et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180608

NAME: (Principal Investigator)	Dr MA Rapuleng, et al
DEPARTMENT:	School of Clinical Medicine Department of Anaesthesia Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Emergence delirium in children undergoing botulinum toxin injections for strabismus correction
DATE CONSIDERED:	29/06/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Ms H Perrie
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	27/06/2019

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore reports and re-certification will be due early in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature — Date: 30/06/2019

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

5.2 Graduate studies approval

WITS UNIVERSITY

DEPARTMENT OF ANAESTHESIOLOGY
UNIVERSITY OF THE WITWATERSRAND,
JOHANNESBURG
Tel.(011)933-9334/5 / Fax (011)933-1843

FACULTY OF HEALTH SCIENCES

28 May 2019

Ms Zanele Ndlovu
Administrative Officer
Human Research Ethics (Medical)

RE : DR ALETTA RAPULENG STUDENT NUMBER 1823395

I herewith grant permission to Dr Aletta Rapuleng to conduct the study titled "Emergence delirium in children undergoing botulinum toxin injections for strabismus correction" in the University of the Witwatersrand Department of Anaesthesiology.

With Kind Regards

Yours sincerely

DR D LINES
PRNCIPAL SPECIALIST AND ACTING HEAD
OF DEPARTMENT OF ANAESTHESIA
UNIVERSITY OF THE WITWATERSRAND

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

06 January 2021
Person No: 1823395
PAG

Dr MA Rapuleng
3583 Zamdela
Ssolburg
1949
South Africa

Dear Dr Moitoi Rapuleng

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Emergence delirium in children undergoing botulinum toxin injections for strabismus correction* 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

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 3rd June 2019

TITLE OF PROJECT:

Emergence delirium in children undergoing botulinum toxin injections for strabismus correction.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr A Rapuleng

Department: Anaesthesiology

Supervisor : H Perrie

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
Date: 3/6/2019

.....
Approved/~~Not Approved~~
Hospital Management
Date: 03/06/2019

5.3 Turnitin report

1823395:Review_turnitin_.docx

ORIGINALITY REPORT

8%	5%	10%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Zainub Jooma, Helen Perrie, Juan Scribante, Thomas Kleyenstuber. "Emergence delirium in children undergoing dental surgery under general anaesthesia", Pediatric Anesthesia, 2020 Publication	1%
2	Dahmani, Souhayl, Honorine Delivet, and Julie Hilly. "Emergence delirium in children : an update", Current Opinion in Anaesthesiology, 2014. Publication	1%
3	associationofanaesthetists-publications.onlinelibrary.wiley.com Internet Source	1%
4	academic.oup.com Internet Source	1%
5	Bong, C. L., E. Lim, J. C. Allen, W. L. H. Choo, Y. N. Siow, P. B. Y. Teo, and J. S. K. Tan. "A comparison of single-dose dexmedetomidine or propofol on the incidence of emergence delirium	1%

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

18th February, 2021

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

Dear Madam,

Re: M Med: **Emergence delirium in children undergoing botulinum toxin injections for strabismus correction**

Dr Aletta Rapuleng, student number: 1823395, has submitted her research report to Turnitin which revealed a similarity index of 8%. 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,

H Perrie

Helen Perrie
Supervisor