Emergence delirium in children undergoing dental surgery under general anaesthesia

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Declaration

I, Zainub Jooma, declare that this Research Report is my own, unaided work. It is being submitted in partial fulfilment of the requirements 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.

Signed: ……………………………………..

……… day of ………………….. 2017 in Johannesburg.

To my father, Ahmed Unoos Jooma who was my greatest believer.

1948-2002

Abstract

Background: Emergence delirium (ED) is a well described complication in paediatric anaesthesia, occurring more often in short surgical procedures using volatile anaesthetics with a rapid recovery profile. Dental surgery is often performed under general anaesthesia in children who would not tolerate dental chair procedures, those with special needs or requiring extensive dentistry. The occurrence of ED in these children at a regional academic hospital was not known.

Aim: The purpose of this study was to describe the occurrence of ED and the associated risk factors in children undergoing elective dental surgery at Rahima Moosa Mother and Child Hospital.

Methods: A prospective, descriptive study of healthy children aged two to six years undergoing elective dental surgery under general anaesthesia was undertaken. Patients were anaesthetised using standardised research protocols. Assessments included: demographics of the child and caregiver, child anxiety at induction using the modified Yale Preoperative Anxiety Scale, intraoperative events and Paediatric Anaesthesia Emergence Delirium score in the recovery room. Data were assessed for associations and correlations.

Results: Ninety-one children with a mean age of 43.4 (SD=10.4) months were included in the study. Anxiety was present in 69.2% at induction and ED was found in 51.6% of the patients. Children with ED required an increased number of interventions in the recovery room ($p < 0.0001$). No association was found with age, gender, education level of the caregiver, number of dental interventions, duration of anaesthesia, intubation status in the recovery room and time to discharge. Correlations between ED and anxiety, age and duration of anaesthesia were not significant.

Conclusions: ED occurs commonly after general anaesthesia for dental surgery but no associated risk factors could be identified. The majority of the children presenting for dental surgery are anxious. Children with ED require more interventions in the recovery room but few require pharmacological treatment.

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List of Abbreviations

ED: emergence delirium

PAED: Paediatric Anaesthesia Emergence Delirium

MRI: magnetic resonance imaging

USA: United States of America

IV: intravenous

EEG: electroencephalogram

BIS: bispectral index

FLACC: Face, Legs, Activity, Cry and Consolability

CHEOPS: Children's East Ontario Pain Scale

CHIPPS: Child and Infant Postoperative Pain Scale

GABA: gamma-amino-butyric acid

mYPAS: modified Yale Preoperative Anxiety Scale

STAIC: State-Trait Anxiety Inventory for Children

OR: odds ratio

UK: United Kingdom

PMB: postoperative maladaptive behaviour

Section 1 Literature Review

1.1 Introduction

The literature review will give a background to the problem at hand, provide historical findings, define emergence delirium (ED) and note the incidence, proposed pathogenesis and risk factors. Patient symptoms at presentation and differentiation from pain will be described. Relevant scoring systems for the diagnosis of ED and anxiety will be discussed. Strategies for prevention (non-pharmacological and pharmacological), management options and long term consequences will be described. A brief description of the relevance of ED in dental surgery will be provided.

1.2 Background

"A crying child in the recovery room is not a problem; it's no big deal. It is certainly a sign of a patent airway!" (1) . This is a statement made by a colleague of Novac (1) in an anaesthesia blog commenting on prevention of ED in paediatric patients.

The child has just arrived in an unfamiliar environment and cannot grasp what has just happened. The parent does not know what to make of this incoherent behaviour. The attending anaesthetist appears to have administered a poor anaesthetic. The recovery room personnel have to pacify this inconsolable child. The other patients in the recovery room do not know how to react to the thrashing child that has just arrived. This is ED.

Surgery has been described as a particularly difficult life experience for children and parents (2, 3). ED is a well described complication in paediatric anaesthesia, more often occurring in short surgical procedures using volatile anaesthetics with a rapid recovery profile (4). While ED is self-limiting, the experience is unpleasant. It is known to cause distress to the patient, parent and attending anaesthetist as well as resulting in parental dissatisfaction (4-6).

A greater emphasis is being placed on patient satisfaction in the assessment of healthcare provision (7) . Integrated perioperative care extends beyond the pharmacological and physiological management aspects and includes the psychological component as well (8). Apart from the short term discomfort, ED has been associated with long term maladaptive behaviours (9). As such, it has been of interest in anaesthesiology literature in recent years with a spate of publications on this subject (8, 10).

1.3 History

ED is not a new phenomenon. It was first described by Eckenhoff et al (11) in the sixties following an observational study of over 14 000 patients between the ages of 3-70 years old. Postanaesthesia excitement, as it was then referred to, characteristically presents with irrational speech, moaning, crying, restless behaviour and disorientation (11). The extreme form of this condition was reported in this study as "wild thrashing, shouting and screaming". From this early data, young age presented as a risk factor for ED with a 12-13% incidence in the 3-9 year olds compared to an overall incidence of 5.3% (11).

1.4 Definition

Delirium is defined in the Diagnostic and Statistical Manual of Mental Disorders V as a disturbance in attention and awareness by the following criteria:

- "disturbance in level of awareness and reduced ability to direct, focus, shift or sustain attention;
- disturbance of cognition;
- disturbance develops over a short period of time." (12)

ED is considered a separate entity due to its specific time period of onset; however features from the Diagnostic and Statistical Manual of Mental Disorders V criteria are generally found in the descriptions. No uniform definition has been formulated due to the heterogeneity of presentation.

Authors have described ED as a state of mental dissociation; others have stated "irritable, uncompromising, uncooperative, incoherent and inconsolable crying, moaning, kicking and thrashing" behaviour (13, 14). Sikich and Lerman (15) defined ED as "a disturbance in the child's awareness of and attention to his or her environment with disorientations and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in the immediate postanaesthesia period." Combative and harmful behaviour requiring physical restraint and paranoid delusions have also been described (16, 17).

An observational study conducted by Malarbi et al (18) to characterise the behaviour of children with ED typically found the following behaviours associated with ED: "screaming, thrashing, kicking, moving arms non-purposefully, arching of the back, tilting the head backwards, staring rather than direct gaze and less likely to be consoled, responsive or purposeful".

Emergence agitation was coined to describe a milder form of the condition; the literature however uses the terms ED, emergence agitation and postanaesthesia excitement or agitation interchangeably (19, 20). ED will be used in this study to encompass all postoperative behaviour changes that are referred to as emergence agitation, postanaesthesia excitation or ED in the literature.

ED occurs early in the recovery period (mean 14 ± 11 minutes) and lasts up to 30 minutes (16). In a study by Cole et al (21) 13% of children had ED immediately postoperatively; this had decreased to 8% by 20 minutes.

While ED is usually a self-limiting phenomenon (13), it is distressing to the caregivers, the patient and the attending anaesthetist. Patients may inflict self-injury, injury to the surgical site, remove intravenous (IV) lines, drains or dressings (5). Parental dissatisfaction and distress may result and additional nursing care is often warranted (16).

1.5 Incidence

The incidence of ED varies from 10-80% in the literature (13, 21, 22); the wide variation is attributed to different scoring systems and different threshold values for assessing the presence of ED in the recovery room.

Eighteen scoring systems that were used in the literature could be identified (23). The three most widely used are the Paediatric Anaesthesia Emergence Delirium scale (PAED), the Cravero emergence agitation scale (24-26) with minor variations (21) and the Watcha behaviour scale for ED (27) with minor variations (28, 29). Within the PAED scale, a number of different thresholds have been used in different studies, making comparability difficult (15, 22, 29, 30).

In a study of 32 patients undergoing magnetic resonance imaging (MRI) in the United States of America (USA) by Cravero et al (24), a high and low threshold definition was used based on the emergence agitation scale level 5 or level 4. High threshold (level 5) was described as thrashing behaviour requiring restraint for more than three minutes, while low threshold (level 4) was crying for more than three minutes. The incidence of ED in the sevoflurane group compared to the halothane group was found to be 80% versus 12% using the high threshold definition and 33% versus 0% using the low threshold definition.

Cole et al (21) studied 260 patients in the USA undergoing abdominal or perineal surgery with a caudal block. An incidence of ED of 10% was found using disorientation and

restlessness as the criteria for ED; when inconsolable crying was added, the incidence increased to 30%.

A difference in incidence between developed and developing countries could not be clearly identified. The lowest incidence of 10.4% was described in a study by Bong et al (22) conducted in 316 paediatric patients undergoing elective outpatient surgical procedures in Singapore. In contrast, in a study conducted in Japan, 16 children undergoing repeat retinal examination under anaesthesia were studied in a two-period study undergoing the same surgical procedure using a different anaesthetic regimen each time; an ED incidence of 38% was found in the sevoflurane group vs. 0% in the propofol group (31). Liang et al (32) found an incidence as high as 63.3% in 90 children undergoing ophthalmological surgery in China.

A survey was conducted by Almenrader et al (33) in Italy and the United Kingdom to gauge anaesthesiologists approach to ED and its current understanding. The anecdotal incidence estimated by the respondents of both countries was <10%. Studies conducted in the developed world showed findings inconsistent with this observation (20, 21, 24-26, 32-34).

A study conducted in the United States of America in 45 children undergoing subumbilical surgery under general anaesthesia with a caudal block revealed an incidence of 50% (34); a similar study conducted on 216 children by Locatelli et al (20) in Italy found an incidence of 25%. Another study carried out in the USA on 179 children undergoing dental procedures showed an incidence of 29% (35); in a similar study in 102 children in the United Kingdom, an incidence of 13% was found by Beringer et al (36).

A similar inconsistency was found in studies in the developing world. A study in Egypt in 70 children undergoing adenotonsillectomy found an incidence of 72% (37). Gooden et al (5) showed an overall incidence of 19.8% in 145 children undergoing different surgical procedures at a specialist children's hospital in Jamaica. In India, Singh et al (38) looked at 75 children undergoing subumbilical surgery with caudal block receiving a different volatile based anaesthetic; a cumulative incidence of 28% in the three groups was found.

It is difficult to draw any inferences from this data as the study methodologies are different and the surgical procedures as well as control of confounding factors are inconsistent. However the wide variability suggests that there are no apparent associations between developed or developing countries and the incidence of ED.

1.6 Pathogenesis

The pathogenesis of ED had not been fully elucidated. The immaturity of the child brain and lack of ability to adapt to a changing environment may have a role to play (39). On a physiological basis, Constant et al (40) demonstrated that the electroencephalography (EEG) patterns evoked during sevoflurane anaesthesia mimic the patterns displayed in epilepsy. Halothane was found to have a different EEG pattern to sevoflurane, desflurane and isoflurane; in addition halothane is also found to have a lower incidence of ED compared to the other volatile agents (19).

The degradation products of sevoflurane have not been found to be neurotoxic, nor is there evidence of drug interactions that may trigger ED (13). Literature on neurotoxicity from metabolites of the other volatile agents could not be found.

Jacob et al (41) looked at the cerebral metabolic profile in children undergoing magnetic resonance imaging with either sevoflurane or propofol anaesthesia. The sevoflurane group showed a significantly higher rate of ED as well as higher levels of cerebral lactate and glucose. The higher lactate levels were postulated to indicate increased neuronal activity, increased glycolysis and "astrocytic lactate shuttling" or mitochondrial dysfunction. This may interfere with return of normal brain connectivity required for cognition on awakening from anaesthesia (41).

A positive correlation between the brain lactate and glucose levels and the PAED score (used to diagnose ED) was found, suggesting that higher cerebral lactate may predict ED. This suggests that the sevoflurane has a different effect on brain networks and metabolic activity and may provide some insight into the genesis of ED (41).

1.7 Risk factors

A number of risk factors have been associated with the development of ED, namely young age, specific surgical procedures, pain, rapid emergence from anaesthesia, type of anaesthetic agent, preoperative anxiety, child temperament and adjunct medication. No significant gender association was identified (5, 36, 42, 43). No literature was identified examining the association of parental education and ED.

1.7.1 Age

Younger children are more vulnerable as they are psychologically immature; awakening in an unfamiliar environment is distressing. Younger age is associated with a greater incidence of ED postoperatively (21, 35). Aono et al (28) found that 40% of preschoolers (3 - 5 years) compared to 10% of school going children (6 - 10 years) undergoing sevoflurane anaesthesia with adequate caudal block for urologic surgery experienced ED. Gooden et al (5) found a three times greater odds (OR 3.3, 95% CI 1.2-8.6; p=0.01) of developing ED in the 3 - 6 year olds compared to the 7 - 10 year olds. In a study by Pryzbalo et al (42), Diagnostic and Statistical Manual of Mental Disorders V criteria was used to diagnose ED; a significantly higher number of children less than five years (62 months) showed altered behaviour .

Geriatric patients and preschoolers show a similar susceptibility for the development of delirium. In the elderly, neuronal loss occurs in the neocortex and hippocampus resulting in decreases in noradrenalin, acetylcholine, dopamine and Y-amino butyric acid (GABA). Conversely, the developing brain shows increases in neurons and synaptic connections. Hippocampal maturation and input of cholinergic neurones play a role in memory expression. Susceptibilities for the development of ED may lie in cholinergic function in the elderly and subcortical cholinergic input into the hippocampus and cortex in younger children (44).

1.7.2 Surgical procedure

No meta-analysis could be identified in the literature citing the surgical risk factors for the development of ED. However, in a review by Voepel-Lewis et al (16) otorhinolaryngology and ophthalmology procedures carry the highest risk. The authors found a 26% and 28% incidence respectively in a cohort study. Eckenhoff (11) postulated that a "sense of suffocation" after emergence from head and neck procedures may have a role to play.

Specific studies in dental procedures are limited. Konig et al (35) found a significant difference in the incidence of ED and the invasiveness of dental procedures (p=0.01); a weak positive correlation with the PAED score was found with duration of surgery (r_s=0.16, p=0.03) and premedication with midazolam (r_s=0.18, p=0.02). In the same study, history of psychiatric, behavioural and developmental problems showed no significant change in the PAED scores (35). Beringer et al (36) similarly found a significant increase in the PAED score and number of teeth extracted (p=0.019), younger age (p=0.009) and previous traumatic experience with doctors or dentists (p=0.006); no significant differences were found with gender, history of previous a general anaesthetic and history of behavioural problems.

Faulk et al (45) found no association between ED and gender (p=0.14), anxiety (p=0.31) and time to discharge(p=0.92); additional nursing intervention was however needed in the recovery room if ED was present (p<0.001).

Aouad et al (30), in a study investigating the effect of IV propofol at the end of an ophthalmologic procedure to reduce ED, demonstrated that more invasive surgery is associated with increased postoperative agitation (p=0.003). In this study, bilateral strabismus surgery was found to cause more ED than unilateral surgery.

A study to compare the length of unconsciousness, as assessed by bispectral index ™ (BIS) monitors and development of ED found no significant association between the length of time of adequate anaesthesia depth as assessed by BIS values and the incidence of ED (p=0.68). Voepel-Lewis et al (16) also found no association between duration of anaesthesia and ED. However another study contradicts these findings; a longer anaesthetic and longer surgery duration being positively correlated (r=0.34; p=0.001) with ED in children undergoing strabismus surgery (46). The contrasting findings may be accounted for as different surgical procedures were undertaken in both studies and the assessment for ED differed.

Rashad et al (47) found that the incidence of ED with sevoflurane anaesthesia increased from 20% at five minutes after recovery room admission to 40% at 30 minutes. This study was conducted in children undergoing elective hypospadias surgery under general anaesthesia with a caudal block. This is in contrast to the findings of Cole et al (21) that found a short-lived duration of behavioural changes in the recovery room, with a decreasing incidence of ED with time (21). The different assessment scales for ED and use of additional drugs in these studies may account for the differing observed duration and pattern of ED.

1.7.3 Pain

Pain is a confounding factor in the diagnosis of ED. The Face, Legs, Activity, Cry and Consolability scale (FLACC), Children's East Ontario Pain Scale (CHEOPS) and the modified version of the CHEOPS, and the Children's and Infants Postoperative Pain Scale (CHIPPS) are validated scales to assess postoperative pain. Similar behavioural patterns are assessed in these scales as in the ED scale; thus differentiating pain from delirium postanaesthesia can be challenging (18, 19, 48).

This discrepancy is apparent in the variable findings in the literature. Some studies have found higher pain scores in the patients that exhibit ED (38) while others have found no association between postoperative pain assessment and ED (37, 49). ED has been

described in studies where caudal blocks have been used for pain control (28, 50-52) and in pain free procedures (24, 31, 53). Wells et al (17) reported that anxiolytic premedication and sufficient analgesia did not prevent the development of ED. A similar finding was reported by Voepel-Lewis et al (16) who found that 98% of children with ED had received intraoperative analgesics. Pain is postulated to confound the diagnosis of ED in short procedures as analgesics have not had sufficient time to reach their peak effect (4, 10).

Aouad et al (30) found no significant difference in pain assessment of children undergoing ophthalmological surgery who were treated with a bolus of propofol before the end of surgery as compared to those treated with saline.

Watcha et al (27) studied the effect of pre-emptive analgesia in children undergoing bilateral myringotomy; pain scores were found to be lower in the group that received pre-emptive ketorolac. Additionally, no difference in ED was found. Similar effects of pre-emptive analgesics have been described in other studies (54-56) .

Singh et al (38) compared the incidence of ED after sevoflurane, isoflurane and desflurane anaesthesia after effective caudal block. A positive association was found between ED and higher pain scores (assessed by the FLACC score). This was despite multimodal analgesia with an adequate caudal block and pre-emptive rectal paracetamol. Not all the patients with higher FLACC scores had ED and not all the patients with ED had higher FLACC scores. This suggests that the features assessed in the ED and pain scales cannot definitively differentiate pain from delirium.

1.7.4 Rapid emergence

Rapid emergence from anaesthesia into an unfamiliar environment has been cited as a risk factor for ED. This especially occurs in young children that are frightened by the strange environment upon awakening (43). In short surgical procedures, analgesics may not have taken effect (4).

The "rapid recovery" characteristic of the newer volatile agents (sevoflurane and desflurane) can be attributed to the low blood gas partition coefficient, allowing for rapid emergence from anaesthesia due to faster washout of the volatile agents (23). Sevoflurane is commonly used as the induction and maintenance volatile agent in paediatric anaesthesia due to its pleasant smell, favourable cardiovascular profile and non-irritant effect on the airway (47). Attributed to this faster emergence, sevoflurane was described to be nine times more likely to cause ED than halothane in a study by Cravero et al (25).

Desflurane has the lowest blood gas partition coefficient of the volatiles with the fastest emergence times. Its pungent, irritant odour limits its use in inhalational induction in paediatric anaesthesia (57). A number of studies have shown a higher incidence of ED with desflurane as compared to other volatile agents (34, 50, 60).

The mechanism of action of volatiles has not been established. The end result produces effects in the central nervous system causing amnesia, lack of movement and dampened sympathetic response. Three theories have been postulated. The Meyer-Overton hypothesis assumes that volatiles act on lipid membranes distorting integrity and inducing these effects. The 5-Angstrom Theory postulated that the volatiles act at two sites; volatiles with these sites 5-Angstroms apart are the most potent. The receptor mediated effects may be either excitatory (serotonin, glutamate or acetylcholine) or inhibitory (nitric oxide) or voltage gated channel effects (57).

A review of the literature by Key et al (43) compared the blood gas solubility of the different volatile agents with the incidence of ED. This is illustrated in Table 1.1. Volatiles with lower blood gas partition coefficients are usually associated with rapid emergence from anaesthesia and are more likely to show a higher incidence of ED.

Table1. 1 ED incidence of different volatile agents (43)

Inhalational agent	Blood gas solubility	ED incidence
Halothane	2.5	26%
Isoflurane	1.46	32%
Sevoflurane	0.65	10-50%
Desflurane	0.42	50-80%

Short time to awakening proved to be predictive for the development of ED (14 ± 14 minutes versus 26 ± 23 minutes; p=0.0001) in a study by Voepel-Lewis (16). Oh et al (58) compared the effect of immediate versus gradual cessation of sevoflurane on completion of surgery with the incidence of ED. Delayed recovery achieved by gradual decrease in sevoflurane concentration showed no significant difference in ED incidence.

A number of other studies have documented the effect of different volatiles. Table 1.2 shows the incidence of ED and other noteworthy findings in each study.

Studies have also examined the concomitant use of nitrous oxide with sevoflurane to decrease ED. Sibata et al (59) compared the use 100% oxygen with oxygen and nitrous oxide during the washout phase after sevoflurane anaesthesia. The ED assessment was significantly lower in the group that used nitrous oxide (p<0.01). It was speculated that the remaining sevoflurane at emergence causes ED; thus nitrous oxide prolongs hypnosis until sevoflurane concentrations have reached a level where ED would not occur (59).

Table1. 2 Studies comparing the ED findings with different volatiles

Author	Year	Study description	Study type	Findings
Davis et al (34)	1994	Des vs Halo (n=45) Subumbilical surgery and caudal	Randomised single blind	Des 50% vs Halo 21% (p=0.09)*
Wellborn et al (60)	1996	Sevo vs Des vs Iso (n=80) Minor ENT surgery	Randomised single blind	Des 55%, Sevo 10%, Halo 25% Recovery and emergence faster with Des
Cravero et al (24)	2000	Sevo vs Halo (n=32) no surgery (MRI)	Randomised single blind	Sevo 33% vs Halo 0% (p=0.001)*
Cravero et al (25)	2000	Sevo vs Halo (n=43) Bilateral myringotomy tube insertion	Randomised single blind	Sevo 57% vs Halo27% (p=0.047)*
Weldon et al (51)	2004	Sevo vs Halo (n=80) Subumbilical surgery and caudal	Randomised single blinded	Sevo 27% vs Halo 5% (p<0.05)*
Meyer et al (53)	2007	Sevo vs Iso (n=59) Subumbilical surgery and caudal	Randomised single blinded	Sevo 30% vs Iso 34% (p=0.79) More analgesics used in sevo group (p=0.07) *
Singh et al (38)	2012	Sevo vs Des vs Iso (n=75) Subumbilical surgery and caudal	Randomised double blind	Sevo 40%, Des 28%, Iso 10% (p=0.168) Sevo and des shorter emergence time (p=0.001)* ED associated with higher pain scores (p=0.034)* No difference in rescue treatment
Locatelli et al (20)	2013	Sevo vs Des (n=260) Subumbilical surgery and caudal	Randomised single blind	25% ED Des = Sevo Des shorter duration of ED
Sethi et al (50)	2013	Sevo vs Des (n=88) cataract surgery with subtenon block	Randomised double blinded	Sevo 18% vs Des 20% (p=1.000) Des faster emergence No correlation with pain (p=0.152) and anxiety- mYPAS (p=0.870)
Costi et al (61)	2014	Sevo vs other GA (n>4000) All surgical types	Systematic review	Halo RR=0.51 [95% CI 0.41-0.63] *a Iso RR=0.76 [95% CI 0.46, 1.23] b Des RR=1.46 [95% CI 0.92, 2.31] b (compared to sevo)

Sevo- Sevoflurane   Halo- Halothane   Des- Desflurane   Iso-Isoflurane

[a] Moderate quality evidence   [b] High quality evidence   * Significant

1.7.5 Type of anaesthetic

Comparison of volatile based anaesthesia versus IV anaesthesia, mainly propofol, has revealed marked differences in the incidence of ED (43, 62-64). The reasons for this are not understood. The difference in the EEG patterns evoked by volatile anaesthetics compared to IV agents and the unique "metabolomic signature" of both the inhalational and IV agents may provide some insight into the reasons for this (40, 41).

Propofol is a widely used induction agent that works on the $GABA_A$ channel. It has a high blood-tissue solubility, with an onset of action within 30 seconds and a distribution half-life of 2 - 4 minutes (57). Its pharmacokinetic profile makes it ideal for use in outpatient surgery due to its smooth recovery profile.

Kanaya et al (63) carried out a meta-analysis of randomised controlled trials to compare volatile based anaesthesia with IV propofol based anaesthesia with regards to ED. Fourteen trials comprising of over 500 patients in the treatment and control groups were analysed.

Propofol based anaesthesia showed a significantly lower odds of 0.25 (95% CI 0.16-0.39; p=0.000). Sub-analysis was conducted on the results to eliminate confounding factors such as surgical type, postoperative pain and age. Propofol was found to significantly decrease the incidence of ED in the 7 years and younger group, in adenotonsillectomy and in non-painful procedures (63).

The time to extubation was found to be significantly lower in sevoflurane anaesthesia in this meta-analysis. However, this was not the primary endpoint of most of the studies and thus marked heterogeneity in methods of determining time to extubation means this must be interpreted with caution (63).

In a Cochrane review of inhalational versus IV anaesthesia for outpatient paediatric surgery, sevoflurane showed an incidence of 24.7% versus 11.5% for propofol (OR 2.67, 95% CI 1.14-6.23). The authors noted that the quality of the evidence was low due to the heterogeneity of the studies (64).

Dahmani et al (65) conducted a meta-analysis on pharmacological prevention of ED in trials with sevoflurane or desflurane based anaesthesia. Propofol was found to have an overall protective effect in preventing ED (OR 0.21 95% CI 0.16-0.28; p=0.01); a bolus of propofol at

induction was ineffective while continuous administration or a bolus before the end of surgery was protective (65).

Although the findings of Kanaya et al (63), Dahmani et al (65) and the Cochrane review (64) favoured propofol, the strength of the findings was not consistent. The studies analysed in each review were different in terms of surgery types, methodologies and diagnostic criteria, with both meta-analysis including more recent studies (63-65). This heterogeneity may have accounted for this inconsistency.

Aouad et el (30) demonstrated that a single bolus of propofol versus saline at the end of surgery significantly lowered the ED incidence in strabismus surgery (19.5% versus 47%, p=0.01). Longer emergence times were found with propofol anaesthesia and parental satisfaction was greater after propofol based anaesthesia (30, 31). Hasani et al (62) compared the incidence of ED after propofol versus halothane based anaesthesia. In contrast to the findings with sevoflurane; propofol was associated with a significantly higher incidence of ED than halothane (29.3% versus 9.5%; p<0.05) and a significantly shorter recovery time. This may further support the theory of more rapid emergence associated with a greater incidence of ED.

1.7.6 Preoperative anxiety

Preoperative anxiety has been found to increase the risk of ED as well as postoperative negative behaviours (66). Classical predictors of preoperative anxiety are similar to those associated with ED, namely young age, previous negative surgical experience (36), parental anxiety, temperament of the child (emotional, impulsive, poor sociability), no enrolment in day-care and poor social adaptive potential (67).

Kain et al (68) found that 65% of patients presenting for surgery exhibit anxiety. The peak of anxiety was found to be at the time of mask induction (5, 69). The effect of parental anxiety on child anxiety has shown conflicting results. Behringer et al (36) found no correlation between the child's and the parent's anxiety; in two studies by Kain et al (9, 70) a significant association was found between the two.

The association between preoperative anxiety and ED has been demonstrated in several studies. In a retrospective study, Kain et al (9) established that for each 10 points on the anxiety assessment score, there was a 10% increased odds of ED. A further study by Kain et al (71) showed a higher level of ED in anxious children (p=0.048); additionally these children

experienced more pain, had higher postoperative analgesic requirements and displayed more anxiety and sleeping problems than non-anxious children. Aono et al (28) found an incidence of 74.1% of ED in the group of children with higher anxiety levels. In a prospective study of over 2000 patients, Holm-Knudsen et al (72) found children with anxiety had a relative risk of 1.6 of ED which was statistically significant.

1.7.7 Temperament

Certain personality features may predict a negative response to surgery. Poor adaptability was significantly associated with the risk of developing ED in the prospective cohort study by Voepel-Lewis et al (16). Kain et al (9) found that impulsiveness, poor sociability and emotional behaviour is associated with developing ED. An innate propensity, described as "excitability, responsivity or arousability", seems to exist in some children that predisposes them to higher levels of anxiety preoperatively, ED in the recovery period extending to postoperative behavioural changes (9) .

1.7.8 Adjunct medication

In the earliest identified study, Eckenhoff et al (11) found an increased incidence of ED in patients that received anticholinergics (scopolamine more than atropine) and barbiturate premedication. Benzodiazapenes have shown conflicting results; some studies have shown an increased incidence of ED (21) while other studies have found a reduction in ED or no effect. (13, 19, 65) Residual effects of ketamine, droperidol and metoclopramide may play a role in delirium in adult patients (73). Ketamine was found to be protective in some paediatric studies (54, 74), while others demonstrated higher ED (47). No studies in paediatrics regarding droperidol and metoclopramide were identified.

1.8 Presentation

As described above, the presentation of ED is heterogeneous. In general, the patients are disorientated, crying inconsolably, incoherent and sometimes exhibiting violent behaviour. Of importance to the attending anaesthetist is to exclude other life threatening conditions that may present similarly in the recovery room. Hypoxemia, hypercarbia, hypoglycaemia, airway obstruction, raised intracranial pressure or hypotension can present similarly and must be attended to urgently. Other causes of agitation in children in recovery are pain, hunger, parental separation or bladder distension (23, 75).

1.9 Scoring systems

Assessment of preoperative anxiety and ED is performed by means of scoring systems. A number of different scoring systems for each have been described, although only a few have been validated and are routinely used in the literature.

1.9.1 Preoperative anxiety assessment

Numerous scales have been described to quantify child anxiety. Observational measures, visual analog scales and questionnaires have been utilised; only the most widely used will be discussed below. The modified Yale Preoperative Anxiety Scale (mYPAS) will be used in this study.

The State-Trait Anxiety Inventory for Children (STAIC) developed by Spielberger (76) is regarded as the gold standard for assessing anxiety over the age of five years old. It is a self-report questionnaire taking between five to 10 minutes to complete, making its use in clinical practice tedious. Items are measured on a four-point Likert scale and scores of 20-80 are obtained, with scores higher than 37 indicative of anxiety. It cannot be used to assess anxiety at the time of induction, when it is known that anxiety levels peak (69).

The Yale Preoperative Anxiety Scale was developed by Kain et al (77) in 1995 for use in children older than two years. It is an observational measure of anxiety taking a minute to complete. Five domains of behaviour, namely activity, emotional expressivity, vocalisations, use of parents and arousal are observed. It was designed for anxiety assessment, used at the time of entering the operating theatre with good intra and inter-observer reliability and validity (76, 77).

This scale was modified by the authors in 1997 and tested for reliability and validity against the STAIC (76) . The mYPAS allowed for measurement at four points of the preoperative period namely, in the waiting area, at the time of parental separation, on entry to theatre and at induction (69). It has been used in over 100 studies and has improved comparability between studies (78).

The five original domains of behaviour were examined and modified by a team of anaesthesiologists and psychologists after observing videotapes of child behaviour in the waiting area prior to surgery. More appropriate behavioural descriptions were added. This scale was then tested against the STAIC; a threshold value of 30 on the mYPAS had a

sensitivity of 0.85 and specificity of 0.92 compared to the STAIC. A lower value reduced the predictive values while a higher value increased the false negative rate (76) .

The score is calculated by dividing the rating achieved in each category by the maximum possible rating in that category, then adding the each value and multiplying the sum by 20 {(a/4+ b/6+ c/4+ d/4+ e/4= total } X 20). Scores range from 23.33 to 100; scores greater than 30 indicate anxiousness (76, 79).

Jenkins et al (78) described a shortened version of this scale eliminating the use of parents domain and limiting the points of measurement to the waiting area and at the time of induction only. The shortened version of the scale retained its accuracy compared to the mYPAS and allows ease of use in the research setting (78), but most studies use the mYPAS to assess for anxiousness.

Table1. 3 The modified Yale Preoperative Anxiety Scale (79)

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

1.9.2 ED scoring systems

A variety of assessment tools are applied in different studies to diagnose ED. Lack of conformity and threshold values for diagnosis of ED makes comparisons difficult. Sixteen rating scales and two visual analogue scales were identified in the literature (23).

The PAED scale developed by Sikich and Lerman (15) has been validated in the diagnosis of ED. The other commonly used scales in the literature are the Cravero emergence agitation scale (24) and the Watcha behaviour scale (27, 29). No psychometric testing has been conducted on these two scales (15). The PAED scale will be discussed in more depth; the other two scales will be briefly mentioned.

Cravero et al (24) described a five-point scale depicted in Table 1.4 with a score of 4 or 5 indicative of ED if present for more than 3 minutes. It has the advantage of simplicity; however the authors changed the duration of symptoms to 5 minutes in another study making comparability difficult (26, 29).

Table1. 4 Cravero emergence agitation scale (24, 29)

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

The Watcha behaviour scale, shown in table 1.5, is a four-point scale and ED is defined by a score of 3 or 4 at any time; it has been utilised in several studies (27, 29).

Table1. 5 Watcha behaviour scale for ED (27, 29)

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

In the PAED scale (29), five parameters are measured: eye contact with caregiver, purposeful actions, awareness of surroundings, restlessness and inconsolability. Each parameter is scored by using a five-point Likert scale, with the last two parameters being scored in reverse order. The total is calculated out of 20.

Table 1.6 PAED scale (29)

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

A score of 10 or more is used as a threshold for the diagnosis of ED showing a sensitivity of 0.64 and specificity of 0.86 (15). The interobserver reliability in this study was 0.84 (95% CI 0.79-0.90). Bong et al (22) found a PAEDS score 10 or more was the best discriminator for the presence of ED. The sensitivity in this study was 0.85 and the specificity 0.959.

However, it was found by Bajwa et al (29) with a score of greater than 12, the sensitivity improved to 1.0 and the specificity to 0.945. Pieters et al (80) used a cut-off value of 16 or more as most of the patients in their study had a score of 10 or more but by subjective assessment, ED was not present.

Locatelli et al (20) isolated the delirium components of the PAED score (ED I: eye contact, purposeful actions and awareness of surroundings) from the non-specific components (ED II: restlessness and inconsolability). ED I was recorded as significant if the sum was nine or more; ED II if the sum was five or more. This was then compared to the values obtained from the conventional PAED score; ED was defined as a sum of 10 or more.

ED I scoring showed a sensitivity of 93% and specificity of 94%; this suggests it is a good test to correctly identify ED as well as non-ED cases correctly. Additionally the ED I scores decreased with time as did the PAED assessment scores. On the other hand ED II scoring showed a sensitivity of 34% and specificity of 95%; it thus poorly identified ED cases while

non-ED cases were correctly identified. However, this differentiation of delirium-specific and delirium non-specific scoring has neither been validated, nor widely used (20).

Bajwa et al (29) compared these three most widely used scales with each other and an experienced paediatric anaesthetic observer. It was found that all three scales correlate reasonably with each other. Compared to the Cravero scale, the Watcha scale has a higher correlation with the PAED scale in detecting ED (29). The Watcha scale and a PAED score of more than 12 were found to have the best sensitivity and specificity in diagnosing ED (29). However, other studies have found a cut-off value greater than 10 as the optimal diagnostic threshold for ED (22, 30, 81).

The Watcha scale is a simpler clinical tool than the PAED scale but it is not widely used for the assessment of ED (6). The Cravero scale has the disadvantage of including "crying", a non-specific item that may not be related to ED and thus has a poorer discriminating ability. The PAED scale is the most widely used despite its complexity. The assessment by a trained anaesthetist is still the best diagnostic method (29).

1.10 Differentiation from pain

As described above, a number of congruent features are found in the ED scoring system and the pain scores. The use of pre-emptive analgesics has shown a decrease in the incidence of ED (26, 55, 56, 82). Studies also found that higher PAED scores have been associated with an increase need for rescue treatment in the recovery room (35, 55).

Three pain assessment scales have been validated for use in paediatrics, namely the FLACC, CHEOPS and the CHIPPS scale (18). The last two components on the PAED scale (restlessness and inconsolabilty) may be more reflective of pain rather than delirium. Sikich and Lerman (15), the researchers that developed the PAED scale, noted that the FLACC scale included consolability as a criteria; restlessness was included in all three validated pain scales. It was included in the PAED scale during its development as it showed statistical correlation with the diagnosis of ED (15, 18).

The first three items on the PAED scale attempt to identify the disturbance of consciousness and cognition, central to the diagnosis of delirium. The authors postulated that the assessment of the five items together would be more reflective of delirium than pain (15).

Locatelli et al (20) attempted to deconstruct the PAED scale into delirium specific and delirium-nonspecific criteria. It was found that the first three criteria (delirium-specific) had a

sensitivity of 93% and specificity of 94% in determining ED. This has however not been validated but may potentially provide a more objective delirium-specific measure, eliminating features that can be indicative of pain (20).

Somaini et al (83) conducted a retrospective observational study in children undergoing surgical and nonsurgical procedures to determine which criteria of the PAED scale were suggestive of ED and which of pain. Children displaying "no awareness of surroundings" and "no eye contact" had ED. Fifteen percent of children in this study showed both ED and pain on the FLACC and PAED scores.

Malarbi et al (18) conducted a study to differentiate the behaviours that reflect ED from those that reflect pain or tantrum. An observational study was conducted to compare the behaviours displayed by children on emergence from anaesthesia with a clinical assessment of ED. Surgical and non-surgical procedures were included. The behaviours were then analysed for statistical significance as individual behaviours and cluster behaviours. The "core behaviours of ED" were found to be non-purposeful behaviour, unresponsiveness and eyes averted or staring. It was found that children indicated pain by verbalisation or touching the surgical site; tantrum was identified by combative behaviour and screaming (18).

Further analysis revealed the odds of ED was 19.31 times higher if the child was kicking; purposeful movement had an odds ratio (OR) of 0.03 and consolability of 0.06. Furthermore, children showed a greater likelihood of ED if they had eyes staring or averted (OR 73.71) and displayed non-purposefulness (OR 93.29) (18).

These findings suggest that a more specific scoring system needs to be tested and validated that will more clearly differentiate between pain and emergence delirium. This will provide a "gold standard test" for the assessment of ED and allow for simpler comparability between studies.

1.11 Preventative

Preventative measures can be divided into non-pharmacological and pharmacological. The pharmacological interventions are either as premedication, regional anaesthesia as an adjunct or drugs given intraoperatively. All three will be discussed together as studies show significant overlap in the preventative measures used.

1.11.1 Non-pharmacological

Non-pharmacological strategies are directed at allaying preoperative anxiety. A number of pre-surgical preparatory programs and parental presence have been investigated.

Low sensory environment, distraction techniques and clown doctors have successfully decreased preoperative anxiety. Behavioural modelling programs such as video games, information tours and interactive books have also shown success. The age of the child and the time prior to surgery of different interventions play a role in the usefulness of the intervention (67, 84).

A family based behavioural coaching program, ADVANCE, an acronym for anxiety relief, distraction techniques, video information, adding parental presence, no parental reassurance by, coaching parents behaviour during induction and exposure of the child to the anaesthesia mask, was developed (67). It was found to be more effective than midazolam premedication in reducing anxiety; it also reduced the ED incidence and the need for postoperative analgesia.

Parental presence has been found to be inconsistent in allaying anxiety (39). In a systematic review, eight trials comparing parental presence versus no parental presence were examined; no beneficial effect was found in decreasing child anxiety. Midazolam was found to be superior to parental presence in another study (84).

1.11.2 Pharmacological

A number of adjuncts have been tested in an attempt to reduce ED. Opioids, benzodiazapenes, α-2 agonists, ketamine, propofol, magnesium, serotonergic antagonists and melatonin have been studied (23, 65).

Midazolam premedication allays preoperative anxiety but showed inconsistent results regarding ED (13, 23). In a study by Cole et al (21), midazolam premedication was associated with a nine times greater chance of ED than no premedication. In the meta-analysis by Dahmani et al (65), no protective effect was found, regardless of whether additional analgesics were used or not. The amnesic effect of midazolam at induction may worsen the delirium on emergence likely due to the disorientation caused by the premedication (23). Paradoxically, midazolam may cause excitatory effects and pain may be worsened by its anti-analgesic effect (13).

Premedication with clonidine was found to be superior to midazolam in prevention of ED in another meta-analysis of trials by Dahmani et al (65). In a study by Kain et al (85), melatonin as a premedication was more effective than midazolam in preventing ED in a dose-dependent manner but resulted in less anxiolysis.

Intranasal fentanyl administered to children for myringotomy and tube placement was found to decrease the incidence of ED (23% versus 2%). There was no increase in the time to discharge from the recovery room and no other postoperative complications (56). Finkel et al (82) described similar findings.

Pre-emptive IV opioid administration has been documented. Cohen et al (86) investigated the most effective dose of preoperative fentanyl to prevent ED without adverse recovery characteristics. A dose of 2.5ug/kg was found to be effective; however postoperative emesis occurred in 75% of cases. In a subsequent study, Cohen et al (87) found that preoperative IV fentanyl decreased the incidence of ED with both desflurane or sevoflurane.

The effects of sufentanil, alfentanil and remifentanil on the incidence of ED have also been studied, although studies examining these effects are limited. Bilgen et al (74) found that intraoperative alfentanil did not reduce ED as compared to saline or ketamine. Na et al (88) found that a continuous infusion of remifentanil intraoperatively significantly reduced the incidence of ED. Liang et al (32) showed that intraoperative sufentanil given 20 minutes before the end of surgery reduced ED as effectively as intraoperative fentanyl when compared to the control group. Li et al (89) however found that intraoperative sufentanil significantly decreased ED compared to fentanyl when given as a bolus dose at the beginning of surgery.

Aouad et al (30) described the use of a bolus of propofol of 1mg/kg at the end of surgery. In the treatment group the incidence of ED was decreased significantly and there was greater parental satisfaction but emergence was prolonged.

Davis et al (55) compared the incidence of ED in sevoflurane and halothane anaesthesia with and without preoperative ketorolac. Significantly lower rates of ED were found in the treatment group regardless of the volatile used (halothane 42% versus 12% and sevoflurane 38% versus 14%; p<0.05). The placebo group required more rescue medication (oral acetaminophen) in the recovery room; recovery time and postoperative emesis was no different in the groups.

Both α-2 agonists, clonidine and dexmedetomidine, were evaluated. A meta-analysis conducted by Dahmani et al (65) favoured the use of α-2 agonists over controls to prevent ED (OR 0.23 95% CI 0.17-0.33, p=0.2). Scrutiny of the type and route of administration of α-2 agonists (caudal or IV) and concurrent analgesia still found a protective effect.

Isik et al (53) studied the effects of perioperative dexmedetomidine in children undergoing MRI scans. A single dose of 1 μg/kg was given after inhalational induction with sevoflurane. The incidence of ED in the control group was significantly higher (33.3% vs. 0%). No adverse haemodynamic effects were found in the treatment group. Ghai et al (90) found that a higher dose of IV dexmedetomidine was more effective in reducing in ED. An intra-operative dexmedetomidine infusion also demonstrated lower ED rates (91) .

Khattab et el (54) investigated the use of 2 mg/kg of oral ketamine in children undergoing dental procedures. ED was significantly decreased from 21.7% in the control group to 6.5% in the ketamine group. Rescue fentanyl in the recovery room was decreased in the ketamine group. No difference in time to discharge was noted. Bilgen et al (74) studied the effect of intranasal ketamine versus alfentanil or saline on ED in urological surgery. Significant decreases in ED were noted in the ketamine group (3.8% versus 36% and 40.7%).

Abdulatif et al (37) looked at the use of magnesium sulphate to decrease ED in adenotonsillectomy. The treatment group showed a significant decrease in ED; an incidence of 72% was found in the control group compared to 36% in the treatment group (RR 0.51, 0.31-0.84 95% CI; p=0.004). No differences in the recovery period or postoperative complications were noted.

Dahmani et al (65) found no protective effect of serotonergic antagonists on ED (OR 0.39, 0.12-1.31 95% CI; p=0.56).

1.12 Management

ED is generally a self-limiting phenomenon. The decision to treat depends on the duration and severity of symptoms and the practice of the attending anaesthetist. Importantly, the child must be protected from injury to themselves and to the surgical site (13). Non-pharmacological management can include parental presence and maintaining a quiet environment in which the patient can recover (92) . Almenrader et al (33) found, in a survey of the practice of anaesthesiologists in Europe and the United Kingdom (UK), that 54.4%

waited for spontaneous resolution among the UK participants while in Italy 49.6% preferred to treat ED with midazolam as the first line treatment.

Treatment may be with sedatives or analgesics. The use of opioids, benzodiazapenes, dexmedetomidine and propofol has been described (13, 67). Fentanyl as a rescue treatment has been described in many studies with doses ranging from 0.5 - 2.5 µg/kg IV (35, 54, 60). Propofol as a single bolus of 0.5 – 1 mg/kg IV was used as rescue treatment (51, 65). Beskow et al (93) used midazolam 0.1mg/kg IV in a study of minor surgery comparing sevoflurane and halothane. Use of dexmedetomidine 0.5 µg/kg IV as a single bolus has been described (65, 67). A combination of a benzodiazepine and opioid has also been described but the dosages of each were not stated (16).

1.13 Long term consequences

Perioperative behavioural changes exists on a spectrum from preoperative anxiety, ED and postoperative maladaptive behaviours (PMB) (2, 9). PMB was observed in 78% of children up to two weeks postsurgery (71). Preoperative anxiety and ED were found to be predictors of PMB (9).

PMB included general and separation anxiety, sleep disturbances, eating disturbances, withdrawal, aggression, temper tantrums and disobeying parents (66). New onset enuresis occurred uncommonly (68). Fear of anaesthesia and surgery can develop and this may hamper future medical help seeking behaviour (66, 67).

Kain et al (9) reported an OR of 1.43 of PMB in children exhibiting ED; it was also found that an increase in anxiety scores preoperatively increase the risk of PMB by 12%. The incidence of PMB in another study by Kain et al (66) was 67% at day one and 23% at day 14 post surgery. A study observing long term behavioural changes found 54% of children with PMB at day 14 post surgery, 20% at six months and 7% persisted at one year (68).

The long term outcome of ED has not been established. An association between ED and PMB have been found in the literature but a cause-effect relationship between has not been proven (9).

1.14 Dental surgery

ED in dental surgery in particular is the focus of the study and will be briefly discussed. Dental caries is the most common disease in children worldwide (94). In South Africa, between 45-60% of children require treatment for dental caries with a mean of between two to three teeth requiring attention per child (95). The percentage of these children that would need general anaesthesia could not be found.

Dental anaesthesia in paediatrics is often performed under general anaesthesia in young children who would not tolerate dental chair procedures those children with special needs or patients requiring extensive dentistry (96). Common procedures performed include extraction of deciduous teeth and conservation dentistry, both of which are not painful postoperatively (96).

Surgery is performed after infiltration of local anaesthetics; usually no opioids are administered intraoperatively. Opioids have been shown to decrease the incidence of ED (56, 82). Local anaesthesia during dental surgery eliminates the aspect of pain and the use of intraoperative opioids; therefore ED as a separate entity can be more objectively assessed in this subset of patients.

ED studied in dental patients have reported an incidence of 13 - 29% (35, 36, 45, 54). No studies documenting the incidence of ED in South Africa, in neither the dental surgical group nor any paediatric group, could be identified.

1.15 Conclusion

ED is a well described complication in paediatric anaesthesia, occurring more often in short surgical procedures using volatile anaesthetics with a rapid recovery profile. While it is short-lived, it is distressing to the patient, parent and attending anaesthetist. In the long term, it can cause PMB and negatively impact on future help-seeking behaviour. Recognition of risk factors allows for appropriate preventative interventions.

1.16 References

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Section 2 Author Guidelines

This section details the author instructions for submission to the journal *Pediatric Anesthesia*. The style and formatting of the article in Section 3 is specific to the author guidelines and may differ from the rest of the document.

***Pediatric Anesthesia*'s mission is to advance the science and clinical practice of paediatric anaesthesia, pain management and peri-operative medicine through dissemination of research, education and quality improvement.**

Priority is given to high-quality original research that advances knowledge, safety, organisation or methodology applicable to other settings and countries. We would particularly like to encourage the reporting of randomised controlled trials.

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POLICIES

Ethics

The journal's ethical policies are outlined in the separate document, Ethics Policy of Pediatric Anesthesia. These guidelines must be followed in full.

Consent for publication

Published article: If individuals might be identified from a publication (e.g. from images or description) authors must obtain explicit informed consent from the individual, or parent or guardian for children. Please do not confuse this with consent for the procedure. Consent, or IRB approved waiver of consent is required for studies involving human subjects.

A patient consent form is available in English: Patient Consent Form and in Chinese: Patient Consent Form - Chinese.

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persons that are visible in the Video, or parental consent for any minor visible in the video, to use their image in the video clip.

In addition the author must complete an online broadcast release form available here.

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In line with most journals, *Pediatric Anesthesia* routinely screens all submissions for evidence of redundant material and plagiarism. We expect authors to have read and understood our originality requirements, specified in the journal's ethics policy.

The editorial team will contact the corresponding author if we discover significant overlap with published material.

Disclosures/conflicts of interest

Authors are required to disclose competing interests. A competing interest exists when a primary interest (such as patients' welfare or the validity of research) might be influenced by a secondary interest (such as financial gain or personal rivalry).The corresponding author, on behalf of all co-authors, should ensure the DISCLOSURE section (Submission step 5) is completed at http://mc.manuscriptcentral.com/pan. A statement is required in the main document, at the end of the main text before the references.

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Funding

All sources of funding **must** be disclosed in the Funding section of the paper. List governmental, industrial, charitable, philanthropic and/or personal sources of funding used for the studies described in the manuscript. Attribution of these funding sources is preferred. If in doubt – disclose. For further details, please refer to the Ethics Policy.

For research where no source of funding is declared, include the statement 'This research was carried out without funding.'

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All papers published in *Pediatric Anesthesia* are subject to peer review. Papers that are outside the scope of the journal, that do not comply with the guidelines below or are otherwise judged to be unsuitable by the editor will be rejected without review.

Appropriate papers are usually sent to at least two independent referees for evaluation. Authors are encouraged to suggest reviewers of international standing. Referees

advise on the originality and scientific merit of the paper; the Editor-in-Chief, with advice from the Section Editor, decides on publication. The Editor-in-Chief's decision is final.

PRE-SUBMISSION ADVICE AND PREPARATION

Before submitting your manuscript, ensure that you refer to the requirements below, which explain the file types, structure and supporting information required for a successful submission.

SUBMISSIONS THAT DO NOT CONFORM TO OUR REQUIREMENTS WILL BE UNSUBMITTED. THE EDITOR MAY REJECT YOUR SUBMISSION IF THESE GUIDELINES ARE NOT MET.

Writing should be clear and simple, avoiding excessive use of the passive, and written in good clear 'international' English.

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Figures

Colour space Our printers use the CMYK colour space which refers to the four inks used in printing. RGB is a colour space based on the visible light spectrum and cannot be used for print publication. RGB uses red, green, and blue light added together to produce a broad

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Requirements

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The recording must be continuous and of sufficient quality for us to publish online i.e. no shaking, blurring or interference.
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We do not publish appendices. Supporting material that is too lengthy for inclusion in the full text of the manuscript, but would nevertheless benefit the reader, can be hosted as online-only content, linked to the online manuscript. The material should not be essential to

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All submissions to *Pediatric Anesthesia* should conform to the uniform requirements for manuscripts submitted to biomedical journals, drawn up by the International Committee of Medical Journal Editors (ICMJE) see http://www.icmje.org/.

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All submissions should include the following:

Main document

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6. Corresponding author details should be written after the affiliations list as follows: title (Mr/Mrs/Ms/Dr/Prof), first name(s) written with initials only, and followed by the last name – e.g. Dr. J. E. Smith; add Department, division or unit name in English, (if any), affiliation name, street address, city, postal code, country. Email address;

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   a. What is already known
   b. What this article adds

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10. Six MeSH-compliant keywords (http://www.nlm.nih.gov/mesh) that do not replicate the title

11. Disclosures: Indicate at the end of the text before references: 1. Any necessary ethical approval(s); 2. The source of funding for the study with grant numbers; and 3. Any conflict of interest. You are required to make a statement, even if the answer is 'none'.

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4. Study protocol – the appropriate study protocol (see 'Guidelines on specific papers' below)

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Clinical Implications, please add 1-2 sentences answering the following questions:

a. What is already known about the topic

b. What new information this study adds

A structured abstract of no more than 300 words should include the following: Background; Aims; Methods; Results; Conclusions.

Maximum words – 3500; maximum figures and tables – 6; maximum references – 25. Word counts include all text from the introduction to the end of the text after the disclosures.

Educational Reviews - Educational reviews should have the following structure: Introduction, Main Article, Summary, Reflective questions, References. Present 3-4 reflective questions that the reader should ponder upon when they have assimilated the knowledge within the article.

Summary of no more than 300 words.

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Case reports – only exceptional reports that have important education or safety messages will be considered. Our current rejection rate is 90%. Conclude with 3 learning points for our readers. All case reports require parental/ patient consent for publication.

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Guidelines for specific papers

Randomised clinical trials (RCTs) must conform to the CONSORT statement (http://www.consort-statement.org) on the reporting of RCTs. A flow diagram of subjects, the trial protocol, and the registration details of the trial must be included in the paper, along with and a numbered checklist provided as supplementary material. Clinical trials MUST be registered prior to the start of the trial.

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Section 3 Draft Article

Emergence delirium in children undergoing dental surgery under general anaesthesia

Emergence delirium in dental surgery

Category: Original research report

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What is known about the topic

- Emergence delirium (ED) is a well described complication in paediatric anaesthesia commonly occurring in preschoolers, in otorhinology or ophthalmology procedures and when using volatile anaesthetics with a rapid recovery profile.

What this article adds

- Most children presenting for dental surgery are anxious at induction.
- ED occurs commonly in children undergoing dental surgery; these children require more interventions in the recovery room but few require pharmacological treatment.
- The use of local anaesthetic infiltration intraoperatively limits pain and allows for objective assessment of ED.

Abstract

Background: Emergence delirium (ED) is a well described complication in paediatric anaesthesia, occurring more often in short surgical procedures using volatile anaesthetics with a rapid recovery profile. Dental surgery is often performed under general anaesthesia in children who would not tolerate dental chair procedures, those with special needs or requiring extensive dentistry. The occurrence of ED in these children at a regional academic hospital was not known.

Aim: The purpose of this study was to describe the occurrence of ED and the associated risk factors in children undergoing elective dental surgery at Rahima Moosa Mother and Child Hospital.

Methods: A prospective, descriptive study of healthy children aged two to six years undergoing elective dental surgery under general anaesthesia was undertaken. Patients were anaesthetised using standardised research protocols. Assessments included: demographics of the child and caregiver, child anxiety at induction using the modified Yale Preoperative Anxiety Scale, intraoperative events and Paediatric Anaesthesia Emergence Delirium score in the recovery room. Data were assessed for associations and correlations.

Results: Ninety-one children with a mean age of 43.4 (SD=10.4) months were included in the study. Anxiety was present in 69.2% at induction and ED was found in 51.6% of the patients. Children with ED required an increased number of interventions in the recovery room (p<0.0001). No association was found with age, gender, education level of the caregiver, number of dental interventions, duration of anaesthesia, intubation status in the recovery room and time to discharge. Correlations between ED and anxiety, age and duration of anaesthesia were not significant.

Conclusions: ED occurs commonly after general anaesthesia for dental surgery but no associated risk factors could be identified. The majority of the children presenting for dental surgery are anxious. Children with ED require more interventions in the recovery room but few require pharmacological treatment. [299 words]

Background

The child has just arrived in an unfamiliar environment and cannot grasp what has just happened. The parent does not know what to make of this incoherent behaviour. The attending anaesthetist appears to have administered a poor anaesthetic. The recovery room personnel have to pacify this inconsolable child. The other patients in the recovery room do not know how to react to the thrashing child who has just arrived. This is emergence delirium (ED).

Sikich and Lerman[1] defined ED as "a disturbance in the child's awareness of and attention to his or her environment with disorientations and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in the immediate postanaesthesia period." Some authors have described ED as a state of mental dissociation; others have stated "irritable, uncompromising, uncooperative, incoherent and inconsolable crying, moaning, kicking and thrashing" behaviour.[2-4]

Surgery has been described as a particularly difficult life experience for children and parents.[5] ED is a well described complication in paediatric anaesthesia, more often occurring in short surgical procedures using volatile anaesthetics with a rapid recovery profile.[6] It lasts between 5 to 15 minutes, occurs in the first 30 minutes of recovery post anaesthesia and is associated with a longer stay in the recovery room.[2,7]

While ED is self-limiting, the experience is unpleasant. It is known to cause distress to the patient, parent and attending anaesthetist as well as parental dissatisfaction.[6] The child may also inflict self-harm, disrupt the surgical site and remove intravenous lines or catheters.[3]

The pathogenesis of ED has not been fully elucidated. The immaturity of the child brain and its lack of ability to adapt to a changing environment may have a role to play.[8] Changes in brain area connectivity during anaesthesia have been investigated. Sevoflurane, in contrast to propofol, was found to depress the resting functional brain network to a greater extent during anaesthesia and upon emergence, unilateral rather than bilateral network recovery occurred.[8] The differential central nervous system clearance of volatile agents has been postulated to play a role as ED is known to occur more commonly with agents with a rapid recovery profile.[6,8]

The incidence of ED varies from 10 to 80% in the literature[2,9]; the wide variation is attributed to different scoring systems and different threshold values for assessing ED in the recovery room. Eighteen scoring systems could be identified in the literature.[10] The three most widely used measures are the Paediatric Anaesthesia Emergence Delirium (PAED) scale, the Cravero emergence agitation scale and the Watcha behaviour scale for ED.[11] The PAED scale has been validated for the diagnosis of ED and is the most widely used, improving the comparability of studies.

A number of risk factors for ED have been noted. The rapid emergence from anaesthesia with sevoflurane and desflurane, both newer volatiles with low blood gas solubility profiles, have paralleled an increase in ED.[6] An increased incidence has been found in preschoolers[3], in children who exhibit more impulsive and emotional behaviour[12] and in otorhinolaryngology and ophthalmology procedures.[2] Preoperative anxiety also increases the risk of ED.[12]

Pain is a confounding factor in the study of ED and it exacerbates ED; thus distinguishing between the two can be challenging as many of the features overlap.[1,13] Studies have shown conflicting results when comparing ED and pain.[2,6,14] ED has been found to be lower in studies where pre-emptive analgesia was given, suggesting that inadequate pain control may be a contributing factor.[2] ED has however been described in procedures without surgical stimulation[2,6] and in procedures where pain has been managed by means of regional anaesthesia.[14]

Dental surgery is often performed under general anaesthesia in children who would not tolerate dental chair procedures, those with special needs or requiring extensive dentistry. Surgery is then performed after infiltration of local anaesthesia, thus obviating the need for intraoperative opioids, and limiting postoperative pain.[15] Therefore ED as a separate entity can be more objectively assessed in this subset of patients.

ED can be prevented pharmacologically or non-pharmacologically. Non-pharmacological strategies are directed at allaying preoperative anxiety by minimising sensory environmental stimuli, distraction techniques, clown doctors and other behavioural modelling programs.[6,8] Parental presence has been found to be inconsistent in reducing anxiety.[8]

A number of adjuncts have been tested to reduce the development of ED.[2,8,16] Halothane and propofol are associated with a lower incidence of ED than the newer agents sevoflurane and desflurane.[17] Effective adjuncts include: dexmedetomidine, ketamine, clonidine, fentanyl, midazolam, magnesium sulphate and propofol given at the end of the procedure.[8] Premedication with midazolam has revealed conflicting results; pregabalin and melatonin preoperatively have been found to be effective.[2]

Perioperative behavioural changes exist on a spectrum from preoperative anxiety, ED and postoperative maladaptive behaviours.[12] Behavioural changes include general and separation anxiety, sleep disturbances, eating disturbances, withdrawal, aggression, temper tantrums and disobeying parents.[19] Kain et al[12] reported an odds ratio of 1.43 of exhibiting these behaviours in children with ED when compared to no ED and this can last up to a year.

A greater emphasis is being placed on patient satisfaction in the assessment of healthcare provision.[18] Integrated perioperative care extends beyond the pharmacological and physiological management aspects of anaesthesia and includes the psychological component as well. Although ED is considered benign, it may promote negative future help seeking behaviour[6] and its long term outcome has not been established.

The incidence or risk factors associated with ED is not known in the South African context. This study examines the occurrence of ED and the associated risk factors in children undergoing elective dental surgery at Rahima Moosa Mother and Child Hospital (RMMCH).

Methods

Approval to conduct this study was obtained from the Human Research Ethics Committee (Medical) and other relevant authorities. Written informed consent was obtained from the parents or caregivers on the day of surgery. Children aged six years signed an assent form.

RMMCH is a 338 bed regional academic hospital that has five theatres, one of which is exclusively used for paediatric surgical cases. On average 6700 adult and paediatric cases are performed annually of which approximately 250 are paediatric dental cases.

This study was a prospective, contextual and descriptive study. Children aged two to six years, ASA I or II, presenting for elective dental surgery to RMMCH during the study period were recruited. Exclusion criteria included mental retardation and developmental delay; inability of the caregiver to converse in English or refusal to participate; and allergy or contra-indication to sevoflurane or other study drugs.

A minimum sample size of 85 was calculated to achieve a 95% confidence interval (2-tailed) and a power of 80%. This was based on an ED incidence of 13-29% (19, 20) in children undergoing dental surgery; a minimum expected occurrence of 20% was used.

Each patient received a standardised anaesthetic (as part of the research protocol) by the anaesthetist allocated to the dental list. No premedication was given. The caregiver accompanied the patient into the operating room and remained until the patient was asleep. Standard intraoperative monitoring was used. An inhalational induction with sevoflurane and oxygen was performed. An intravenous line was placed and propofol was given; the dose titrated to effect; to facilitate nasal intubation and a throat pack was placed. Ventilation was controlled to achieve normocapnia. The surgical area was infiltrated with lignocaine. Either intravenous paracetamol or a rectal suppository (paracetamol or non-steroidal anti-inflammatory drug), dosed according to weight, was given intraoperatively. On completion of the surgery, the throat pack was removed and the patient was transferred to the recovery room intubated or extubated as preferred by the anaesthetist; extubation was then done once the patient was fully awake. Parents or caregivers remained with the patient after extubation. The patient was observed in the recovery room by the author (ZJ) or a trained research assistant and the PAED score was recorded. If ED persists in the recovery room, the patient will be treated with intravenous fentanyl (1ug/kg) at the discretion of the researcher or trained research assistant and observed in the recovery room.

The following data were collected: patient demographics, history of traumatic medical experience, history of dental procedure or anaesthesia, preoperative medication, education level of the caregiver, modified Yale Preoperative Anxiety Scale (mYPAS) score at induction, duration of anaesthesia and total number of dental interventions performed. In the recovery room, the following were recorded: the

intubation status and level of consciousness on arrival in the recovery room, PAED score at five minute intervals, duration of ED and time to discharge.

Preoperative anxiety was measured at the time of induction using the mYPAS which was developed by Kain et al (21) and has been validated for use in children two years and older. Scores range from 23.33 to 100; scores greater than 30 indicate anxiousness.

The PAED scale (Table 1) measures five parameters and is scored by using a five-point Likert scale; the total is calculated out of 20. A score of 10 or above is the threshold value for the diagnosis of ED based on the receiver operating characteristic curve methodology, showing a sensitivity of 0.64 and specificity of 0.86 (1). The PAED score was completed at five minute intervals in the recovery room until discharge to the ward and the highest PAED score attained at any time is used to determine ED.

Data were analysed using the Statistica™ 13 program (Statsoft, USA). Descriptive statistics were reported where appropriate. Demographic and procedure-related variables were compared with the development of ED using Chi^2 or Fishers Exact tests depending on the numbers in each group. The mYPAS score, age and duration of anaesthesia were correlated with the highest PAED score using Spearman's rank correlations. The patients' intubation status and level of consciousness on arrival in the recovery room and time to discharge from the recovery room were compared to ED using either the Students t-test or the Mann-Whitney test. A p value of <0.05 was considered statistically significant.

Results

Ninety-two patients were enrolled into the study. One patient was excluded due to deviation from the protocol. The mean (SD, range) age of patients was 43.4 (10.4, 27-72) months. The other demographic variables of the sample are shown in Table 2.

Preoperative self-medication was given to 6 (6.6%) patients by the parents the night preceding surgery. Complications occurred in 7 (7.7%) patients: 5 (71.4%) patients developed laryngospasm (2 (28.6%) required treatment with suxemethonium); low intraoperative blood pressure and postoperative

bleeding each occurred in 1 (14.3%) patient. Of the 7 patients with complications, 3 (42.9%) developed ED.

The median (IQR, range) duration of the anaesthesia was 47.3 (40-52.5, 29-85) minutes and duration of surgery was 23 (18.5-30, 8-60) minutes. The mean (SD, range) number of dental interventions performed was 11 (3.27, 4-21).

ED occurred in 47 (51.6%) patients. The median (IQR, range) PAED score was 10 (8-14, 0-18). Pre-induction anxiety was present in 63 (69.2%) patients. The median (IQR, range) mYPAS score was 40.5 (26.67-51.67, 23.33-100). A comparison between ED and mYPAS was statistically significant (p=0.01), OR 0.3 (95% CI 0.11-0.78); however a weak negative correlation between the mYPAS score and ED score (r_s=-0.19) was found which was not statistically significant (p=0.07). Correlation of ED score with age (r_s=-0.1869, p=0.76) and duration of anaesthesia (r_s=0.2060, p=0.05) were not statistically significant.

No statistical significance was found when comparing gender (p=0.20; OR 1.79 95% CI 0.75-4.25), age (p=0.67), history of traumatic medical experience (p=1.00; OR 1.08 95% CI 0.36-3.29) and previous dental procedure or anaesthesia (p=1.00; OR 1.08 95% CI 0.36-3.29) with ED. Demographic and other procedure-related variables compared to ED are shown in Table 3.

The education level of the caregiver was compared with ED. The proportion of patients with ED was much higher in the primary (100%) and tertiary (73.3%) education level of the caregiver groups as compared to secondary education (44.4%). However, no statistical significance was found when the combined primary and secondary group was compared with the tertiary group (p=0.09; OR 0.33 95% CI 0.1-1.12). The frequency of ED in the different education level of the caregiver groups is depicted in Figure 1.

Sixty-eight (74.7%) of the patients were received in the recovery room intubated and asleep; 15 (16.5%) were extubated and asleep; and 8 (8.8%) were extubated and awake. ED was compared to arrival in recovery intubated or extubated (p=0.22; OR 1.97 95% CI 0.75-5.17) and awake or asleep (p=1.00; OR 0.93 95% CI 0.22-3.97); neither showed statistical significance.

The median (IQR, range) duration of ED was 10 (10-20, 5-35) minutes. Comparison of ED with number of dental interventions (p=0.51) and duration of anaesthesia (p=0.38) showed no statistical significance.

The non-pharmacological methods used in this study to manage ED were physical restraint (to prevent self-harm) and/or consoling by the parent or no interventions were needed. Pharmacological methods to control ED were used at the discretion of the researcher and the trained research assistant only if ED persisted despite consoling by the parent and physical restraint for more than 30 minutes, or if the patient was in danger of self-harm. Intravenous fentanyl was chosen as the pharmacological treatment as it is readily available and cost effective in our setting.

In 43 (47.2%) of the patients either with or without ED, no interventions were needed. There was a statistical significance between the patients with ED and the need for some form of intervention in the recovery room (p<0.0001). Two (4.3%) patients with ED required treatment with fentanyl. Figure 2 illustrates the interventions required in the patients with and without ED.

The median (IQR, range) time to discharge from the recovery room for all patients was 31 (27-37.5, 13-77) minutes. Comparison of time to discharge between the ED and no ED group showed no statistical significance (p=0.15).

Discussion

The purpose of this study was to examine the occurrence of ED in children undergoing dental surgery and to compare demographics and other procedure-related variables for associations and correlations with ED.

An occurrence of ED of 51.6% was found in this study. A wide range has been quoted in the literature, between 10 to 80%[2] attributed to the different scoring systems and thresholds used. In the studies pertaining to dental surgery, the incidence ranged between 13 to 29%[4,19,20], but participants up to the age of 12 years were included. A younger age is associated with the development of ED with preschoolers showing the highest risk.[3,20,22] In our study, children between the ages of two to six years

were included, which may have attributed to the higher occurrence of ED. However, no significant association or correlation between age and ED was found.

Anxiety, as measured by the mYPAS, occurred in 69.2% of the children. It was measured at the time of mask induction when it is known to peak[23] and other studies have found a similar incidence.[3,19] Comparison of ED and anxiety showed a statistical significance; anxiety was associated with no ED. The reason for this paradoxical result is not known. Preoperative anxiety was examined as a secondary objective and thus the sample size was not adequately powered for this variable. ED is a complex phenomenon with an interplay of patient, surgical and parental factors, thus its development may differ in different contexts. Conflicting results have been found in the literature; some studies[4,19] have found no association with anxiety while Kain et al[12] found an association. Studies have also found associations between parental anxiety and child anxiety[8,12] but parental anxiety was not measured in our study.

In our institution, it is not routine practice to prescribe premedication before surgery. Children wait in a playroom outside the theatre prior to surgery and parents or caregivers are present in theatre at induction. The high incidence of anxiety at induction despite this suggests that other non-pharmacological means of allaying anxiety should be considered and premedication could be individualised per patient.

Opioids can be used to prevent or treat ED[2,8,16] and thus administration of opioids were excluded from the standardised anaesthetic administered in our study. In the studies pertaining to dental surgery[19,20], opioids were used as part of the standard anaesthetic which may explain the lower incidence of ED; the avoidance of opioids in our study may account for the higher incidence of ED.

Pain was controlled by local anaesthetic infiltration by the dentist and with paracetamol or non-steroidal anti-inflammatory drugs. An upper limit of six years was used for inclusion in the study, as extraction of deciduous teeth found in this age group is not painful postoperatively.[15] These measures attempts to eliminate pain as a confounding factor to allow for an objective assessment of ED. However, we did not assess pain scores in the recovery room and thus the contribution of pain cannot be entirely excluded.

Gender, history of traumatic experience and previous dental procedure or anaesthesia were not associated with ED in our study. Conflicting results have been found regarding gender and ED. Some studies found no association with gender[3,4,7,19]; a review by Dahmani et al[8] however cites male gender as a risk factor. Beringer et al[19] found male patients and those with history of previous traumatic experience exhibited more negative behaviours after discharge. Fifteen patients in our study reported both a history of previous dental procedure and a history of a traumatic medical experience, but no association with ED was found. We did not investigate postoperative behavioural changes.

We postulated that parental education may play a role in the development of ED. The primary and secondary caregiver level of education groups were combined for analysis as the numbers in the groups were small but no significant association was found when compared to the tertiary group. No studies could be identified that investigated this.

Conflicting results have been found regarding duration of anaesthesia and ED; Gooden et al[3] found no association while Konig et al[20] found a positive correlation, but surgery in this study exceeded 120 minutes in some cases. No correlation was found between ED and duration of anaesthesia in our study, however shorter times were recorded (range 29-85 minutes).

ED has been found to be associated with invasiveness of surgery in both dental[19,20] and non-dental[24] surgery. We found no significant association between the number of dental interventions and ED. The median number of interventions required per patient was 11 (4-21), but as young patients with deciduous teeth only were included, this is not usually painful postoperatively.[15] In another study of ED in dental surgery by Konig et al[20], the median number of interventions were 4 (1-16), but the surgery was more invasive involving extractions and crowns or both, attributing for the association of invasiveness of surgery and ED.

Patients with ED required more interventions in the recovery room. The majority of patients (53.2%) with ED required both restraint and consoling, followed by consoling only (38.3%). Medication was used only as a last resort; it was needed in only two (4.3%) patients with ED in our study. Other studies have also found a greater need for interventions in the recovery room, however more patients were treated pharmacologically, reflecting a different management strategy.[3,4,20]

Patients arrived in the recovery room either intubated or extubated, and either asleep or awake. Emergence would be more gradual for patients who arrived intubated and asleep and a slower wake up time was postulated to reduce ED. However, we found no association with status on arrival in the recovery room and ED. Conflicting results are reported in the literature; Aouad et al[25] reports a negative correlation between time to awakening and ED while Gooden et al[3] found no association with emergence time and ED.

Time in the recovery room was not significantly higher in the ED group in our study. This must be interpreted with caution as discharge from the recovery room is determined by staff availability and discharge was delayed in a number of cases due to staff constraints. Other studies have reported a significantly prolonged time in the recovery room in patients with ED, presumably due to the interventions required and monitoring after medications are given to treat ED.[3,7]

ED occurred commonly in the study population, but no risk factors could be identified. Routine preventative medications could be considered in the dental population due to the high incidence of ED observed. The majority of patients were found to be anxious at the time of induction. As it is not standard practice to prescribe premedication in our institution, implementation of non-pharmacological or pharmacological means to allay anxiety can be considered. Future studies can compare the incidence of ED in other surgical procedures and examine the effects of preventative medications in the dental population.

Limitations

The contextual nature of this study is a potential limitation as data were collected at a single hospital and during dental surgery only. Results may not be generalisable to other populations and other surgical procedures.

Disclosures

No conflicts of interest declared. This research was approved by the Graduate Studies Committee at the University of the Witwatersrand and the Human Research Ethics Committee and was carried out without funding. (3465 words)

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Tables

Table 1 PAED scale (11)

Point	Description	Not at all	A little	Quite a bit	Very much	Extrem ely
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

Table 2 Demographics

Demographics	n (%)
Gender	
Male	58 (63.7)
Female	33 (36.3)
ASA	
I	83 (91.2)
II	8 (8.8)
History traumatic medical experience	15 (16.5)
Previous dental procedure or anaesthesia	15 (16.5)
Premedication	6 (6.6)
Education level of the caregiver	
Primary	4 (4.4)
Secondary	72 (79.1)
Tertiary	15 (16.5)

Table 3 Demographic and other procedure related variables compared to ED

Variable	ED n (%)	No ED n (%)	P value
Gender			
Male	33 (70.2)	25 (56.8)	0.20[#]
Female	14 (29.8)	19 (43.2)	
Anxiety			
Yes	27 (57.4)	36 (81.8)	*0.01[#]*
No	20 (42.5)	8 (18.2)	
State of arrival in recovery room			
Intubated	38 (80.9)	30 (68.2)	0.22[#]
Extubated	9 (10.6)	14 (2.7)	
Awake	4 (8.5)	4 (9.1)	1.00[#]
Asleep	43 (91.5)	40 (90.9)	
Caregiver level of education			0.09[#]
Primary & Secondary	36 (76.6)	40 (90.9)	
Tertiary	11 (23.4)	4 (9.1)	
History traumatic medical experience			1.00[#]
Yes	8 (17.1)	7 (15.9)	
No	39 (82.9)	37 (84.1)	
Previous dental procedure or anaesthesia			1.00[#]
Yes	8 (17.1)	7 (15.9)	
No	39 (82.9)	37 (84.1)	
Interventions in recovery room			
None	2 (4.3)	41 (93.2)	*<0.0001[#]*
Any (restrained, consoled, medication)	45 (95.7)	3 (6.8)	

Variable	Mean (SD) / Median (Range)	Mean (SD) / Median (Range)	P value
Age (months)	45.8 (11.3)	46.8 (9.9)	0.67*
Number of dental interventions	11.4 (3.8)	10.9 (2.1)	0.51*
Anaesthesia duration (mins)	48 (29 - 85)	45 (29 - 74)	0.38$
Discharge time from recovery room	35 (20 - 77)	30 (20 - 70)	0.15$

[#] Fishers exact test   * Unpaired t-test $ Mann-Whitney test   Significant p-value results italicised

Figures

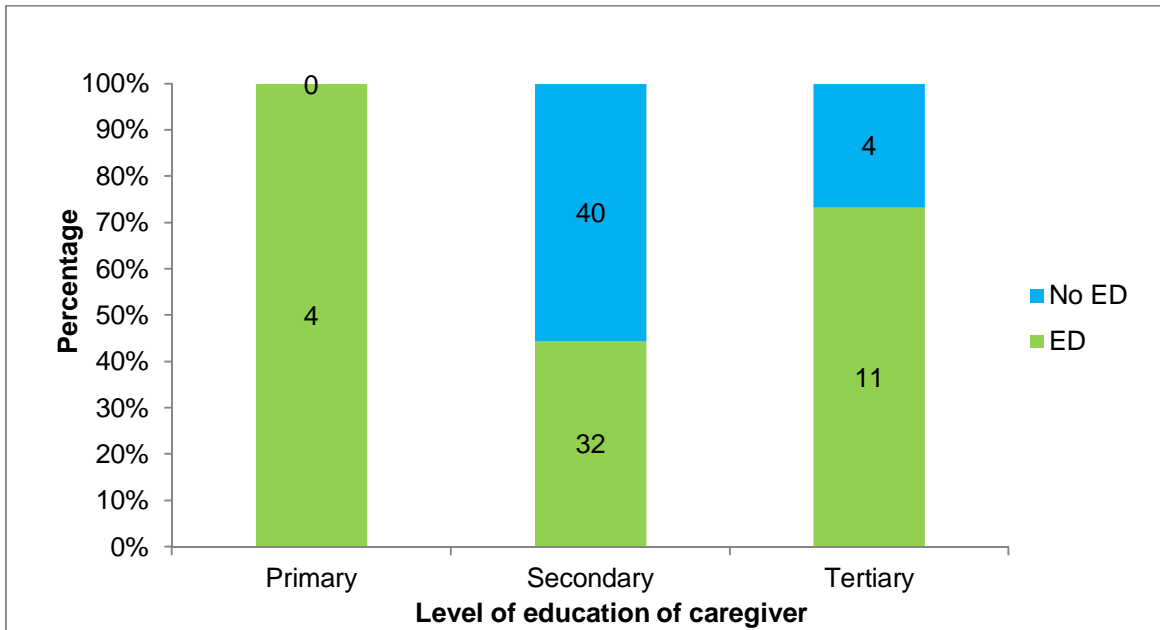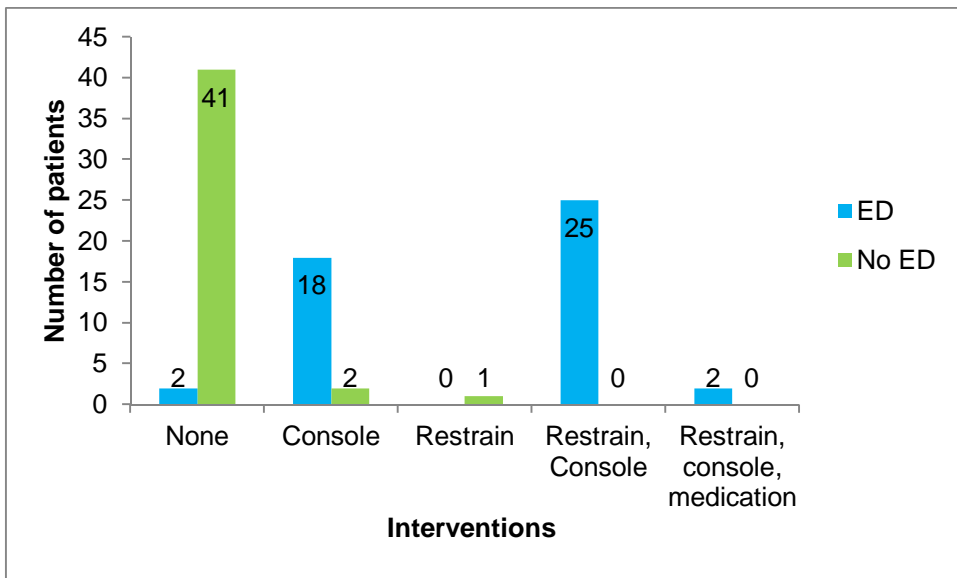Figure 1 ED in the different level of education of caregiver groups

Figure 2 Interventions required in ED and no ED

Section 4 Appendices

4.1 Postgraduate Approval

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050

Fax: 027117172119

Tel: 02711 7172076

Reference: Ms Thokozile Nhlapo

E-mail: thokozile.nhlapo@wits.ac.za

06 February 2015

Dr Z Jooma

Person No: 0301877G

PAG

Middelburg

1050

South Africa

Dear Dr Jooma

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Emergence delirium in children undergoing dental surgery under general anaesthesia* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty'shigher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn

Faculty Registrar

Faculty of Health Sciences

4.2 Ethics Approval

4.3 Permission from CEO of Rahima Moosa Mother and Child Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

Enquiries	: Dr Edward Hank
Tel	: (011) 470 9030/1
Fax	: (011) 477 4117
Email	: Edward.Hank@gauteng.gov.za

Department of Anaesthesiology
University of the Witwatersrand

Dear Dr Jooma,

RE: EMERGENCE DELIRIUM IN CHILDREN UNDERGOING DENTAL SURGERY UNDER GENERAL ANAESTHESIA

Permission is granted for you to conduct the research as indicated in the title above.

The terms under which this permission is granted is contained in the Researcher Declaration form that you have signed. Failure to comply with these conditions will result in the withdrawal of such permission.

It is crucial for you to inform the Research Coordinator, Karen Marshall of the actual start and end dates of your study. This could be done by e-mail.

Should the study commence more than 12 months after receipt of this approval letter you will have to go through the process of applying again.

You are strongly advised to keep a signed copy of the declaration form so as to ensure that the terms of this agreement are complied with at all times.

Yours sincerely,

DR EDWARD HANK
Clinical Manager
2015:05:29

ADDRESS: Cnr. FUEL & OUDSTHOORN STREET CORONATIONVILLE 2093 / PRIVATE BAG X20 NEWCLARE 2112 JHB

4.4 Permission from Head of Anaesthesiology Department

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Department of Anaesthesiology

Rahima Moosa Mother and Child Hospital

Tel: (011) 470---9303

Fax: 0866 170 530

E---mail seanchetty@gmail.com

10 November 2014

Attention: Dr Z Jooma

Dear Dr Jooma

PERMISSION TO CONDUCT RESEARCH

With reference to your communication on the 10th November 2014, regarding conduct of research at RMMCH, I am happy to permit you to conduct this research for your MMed, provided that to are granted approval by the Human Research Ethics Committee of the University of the Witwatersrand and the CEO of the hospital.

Kind Regards

_____

Dr S Chetty

Head: Clinical Unit-Anaesthesiology

Rahima Moosa Mother and Child Hospital

4.5 Permission from Head of the Dental Department

Soraiya Moola   6:48 PM (5 hours ago)

to me

Dear Dr Jooma,
All the best.
Permission Granted.
If you require any assistance,or information
from the dental staff,please don't hesitate to ask.

Thank You
Regards
Dr Moola

On Thursday, March 5, 2015 4:08 PM, Zainub Jooma <zainub.jooma@gmail.com> wrote:

Good day

I am registrar in the Department of Anesthesiology and I hereby request to conduct research as part of the MMED in Anaesthesiology at RMMCH.

The title of my research project is "Emergence delirium in children undergoing dental surgery under general anaesthesia". Data will be collected on children booked for dental procedures on Mondays. The proposed time frame for collection of data is between April-August 2015. I have attached a letter requesting permission and a copy of the protocol.

Please confirm your permission.

Thank you
Dr Zainub Jooma
Registrar Anaesthesiology
083 291 6772

Section 5 Proposal

Emergence delirium in children undergoing dental surgery under general anaesthesia

Zainub Jooma
0301877G

Supervisor: Helen Perrie

                         Department of Anaesthesiology

Co-supervisor: Juan Scribante

                         Department of Anaesthesiology

Co-supervisor: Thomas Kleyenstuber

                         Department of Anaesthesiology

5.1 Introduction

Sikich and Lerman (1) defined emergence delirium (ED) as "a disturbance in the child's awareness of and attention to his or her environment with disorientations and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in the immediate postanaesthesia period." The term emergence agitation was coined to describe a milder form of the condition, although most literature refers to the terms interchangeably (2, 3).

ED was first described by Eckenhoff et al (4) in the 1960s, most notably occurring in head and neck surgical procedures. The incidence was higher in the paediatric population, 12-13%, versus 5.3% in adults (4). However, the incidence quoted in the literature ranges from 10-80% (5-7); the wide variation is attributed to different scoring systems and different threshold values for assessing the presence of ED in the recovery room.

The pathogenesis of ED has not been fully elucidated. The immaturity of the child brain and its lack of ability to adapt to a changing environment may have a role to play (8). Sevoflurane, in contrast to propofol, was found to depress the resting functional brain network during anaesthesia and upon emergence, unilateral rather than bilateral network recovery occurred (8).

Jacob et al (9) examined the cerebral "metabolomic profile" in children undergoing magnetic resonance imaging with either sevoflurane or propofol anaesthesia. A positive correlation between the lactate and glucose levels in the brain and the Paediatric Anaesthesia Emergence Delirium (PAED) score was found in the sevoflurane group. A higher cerebral lactate level indicates enhanced neuronal activity in the brain; this may interfere with return of normal brain connectivity required for cognition on awakening from anaesthesia. This suggests that sevoflurane has a different effect on brain networks and metabolic activity and may provide some insight into the genesis of ED.

A number of risk factors for ED have been noted. The rapid emergence from anaesthesia with sevoflurane and desflurane, both newer volatiles with low blood gas solubility profiles, have paralleled an increase in ED (10). An increased incidence has been found in preschool children (6, 11). Child temperament has also been cited; children who exhibit more impulsive and emotional behaviour and are less adaptable and less social have a higher risk (12). Otorhinolaryngology and ophthalmology procedures carry the highest risk (13).

Preoperative anxiety has been found to increase the risk of ED (14). The classical predictors of preoperative anxiety are similar to those associated with ED (15). The Yale Preoperative Anxiety Scale was developed by Kain et al (16) as an observational measure of anxiety in children older than two years. The scale was modified by the authors in 1997 and tested for validity and reliability (17). This modified Yale Preoperative Anxiety Scale (mYPAS) has been used in over 100 studies and has improved comparability between studies (18). The mYPAS will be used as a measure of preoperative anxiety in this study.

Postoperative pain exacerbates ED and distinguishing between the two can be challenging as the features overlap (1, 2, 19, 20). ED has been found to be lower in studies where pre-emptive analgesics were given, suggesting that inadequate pain control may be a contributing factor (21-23). ED has however been described in procedures without surgical stimulation (24-26) and in procedures where pain has been managed by means of regional anaesthesia (27-30).

Patients present in the recovery room acutely disorientated, inconsolable, with incoherent thrashing movements and incoordination. It is distressing to the patient, the parent and the attending anaesthetist (10, 11, 31). The child may also inflict self-harm, disrupt the surgical site and remove intravenous lines or catheters (11). ED occurs early in the recovery period (mean 14 ± 11 minutes) and lasts up to 30 minutes. It is associated with a longer stay in the recovery room (13).

ED is usually self-limiting and the decision to treat depends on the duration and severity (5). Rescue medication includes analgesics and sedatives, such as benzodiazapenes, opioids, dexmedetomidine and propofol (5, 32).

A number of assessment tools have been applied in different studies to diagnose ED. Lack of conformity of these tools and the use of different threshold values for the diagnosis makes comparisons difficult. The three most widely used measures are the PAED scale, the Cravero emergence agitation five-point scale and the Watcha behaviour four-point scale (33). The PAED scale developed by Sikich and Lerman (1) has been validated for the diagnosis and is the most widely used, improving the comparability of studies (33). The PAED scale will be used to assess for ED in this study.

In the PAED scale, five parameters are measured: eye contact with caregiver, purposeful actions, awareness of surroundings, restlessness and inconsolability. Each parameter is scored by using a five-point Likert scale and the total is calculated out of 20. A score of 10 or

above is the threshold value for the diagnosis of ED based on the receiver operating characteristic (ROC) curve methodology described by Sikich and Lerman (1).

Prevention of ED can be pharmacological or non-pharmacological. Non-pharmacological strategies are directed at allaying preoperative anxiety. Minimising sensory environmental stimuli, distraction techniques, clown doctors and other behavioural modelling programs have successfully decreased preoperative anxiety (10, 34). Parental presence has been found to be inconsistent in allaying anxiety (8).

Pharmacological preventative measures vary. Halothane and propofol are associated with a lower incidence of ED than the newer agents sevoflurane and desflurane (35). Effective adjuncts include: dexmedetomidine, ketamine, clonidine, fentanyl, midazolam, magnesium sulphate and propofol given at the end of the procedure (8). Premedication with midazolam has revealed conflicting results; pregabalin and melatonin preoperatively have been found to be effective (35-37).

Postoperative maladaptive behaviours (PMB) associated with ED have been reported. Behavioural changes include general and separation anxiety, sleep disturbances, eating disturbances, withdrawal, aggression, temper tantrums and disobeying parents (14). Fear of anaesthesia and surgery can develop and this may hamper future medical help seeking behaviour (10, 14, 38). Kain et al (12) reported an odds ratio of 1.43 of exhibiting these behaviours in children with ED when compared to no ED. PMB can persist for up to one year although the long term outcome of ED has not been established (12, 39).

5.2 Problem Statement

Surgery has been described as a particularly difficult life experience for children and parents (40, 41). Perioperative behavioural changes exist on a spectrum from preoperative anxiety, ED and PMB (12, 40). ED is a well described complication in paediatric anaesthesia, occurring more often in short surgical procedures using volatile anaesthetics with a rapid recovery profile (10).

Dental surgery is often performed under general anaesthesia in children who would not tolerate dental chair procedures, those with special needs or requiring extensive dentistry (42, 43). Surgery is performed after infiltration of local anaesthesia, thus obviating the need for intraoperative opioids, and limiting postoperative pain (42).

Pain is a confounding factor in the study of ED as many of the features overlap (1, 2, 19, 20). The use of opioids has been shown to decrease the incidence of ED (23, 44, 45). Dental

extractions and conservation dentistry, the most commonly performed procedures in children, are not painful postoperatively and routinely no intraoperative opioids are used (42). Therefore ED as a separate entity can be more objectively assessed in this subset of patients.

A greater emphasis is being placed on patient satisfaction in the assessment of healthcare provision (46). Integrated perioperative care extends beyond the pharmacological and physiological management aspects of anaesthesia and includes the psychological component as well (38). While ED is self-limiting, the experience is unpleasant. It causes parental dissatisfaction and is distressing to the patient, parent and attending anaesthetist (10, 11, 31). It is considered benign but it has been associated with long term maladaptive behaviours (12) and it may promote negative future help seeking behaviour (14, 38).

No South African studies could be identified that document the incidence or risk factors associated with ED.

5.3 Aim

The aim of this study is to describe the occurrence of ED and the associated risk factors in children undergoing elective dental surgery at Rahima Moosa Mother and Child Hospital (RMMCH).

5.4 Objectives

The objectives of this study are to:
- describe the occurrence of ED in children undergoing dental surgery using the PAED scale;
- describe the preoperative anxiety (at induction) using the mYPAS;
- correlate the development of ED with anxiety, age and duration of anaesthesia;
- describe and/or compare demographic and procedure-related variables with the development of ED;
- describe and compare the state of arrival in the recovery room with the development of ED;
- describe the non-pharmacological and pharmacological management of ED and
- compare the time to discharge from the recovery room of patients with and without ED.

5.5 Research assumptions

The following definitions will be used in the study.

Child: is a person between the ages of 2 and 6 years old.

Caregiver: is the person responsible for providing long-term day-to-day care for the child. This person is allowed to give consent on behalf of a minor (47).

Dental surgery: in this study includes extractions, fillings and pulpotomies only.

PAED scale: is the scoring system developed by Sikich and Lerman (1) to assess ED in the recovery room. It is the objective measure of ED that will be used in this study (Appendix C).

Emergence delirium: is defined in this study as a PAED score of ten or more.

The mYPAS: is the scale validated to assess preoperative anxiety in children (17) (Appendix C).

Anxiety score: anxiousness is defined as a threshold value of more than thirty on the mYPAS scale (17) .

State of arrival: is the level of conciousness and intubation status on arrival in the recovery room either: intubated and asleep; extubated and asleep; or extubated and awake.

ASA Classification: is the American Society of Anaesthesiologists physical fitness classification (48).
- ASA I: a fit, healthy patient.
- ASA II: a patient with mild systemic disease.
- ASA III: a patient with severe systemic disease.
- ASA IV: a patient with severe systemic disease that poses a threat to life.
- ASA V: a patient that is not expected to live more than 24hours irrespective of surgical or non-surgical treatment.

5.6 Demarcation of study field

This study will be conducted in the recovery room of the theatre complex of RMMCH affiliated to the Department of Anaesthesiology at the University of the Witwatersrand. RMMCH is a 338 bed regional academic hospital. The hospital has five theatres, one of which is exclusively used for

paediatric surgical cases. On average 6700 adult and paediatric cases are done annually of which approximately 250 are paediatric dental cases.

5.7 Ethical considerations

Approval to conduct this study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee, Faculty of Health Sciences of the University of the Witwatersrand.

The Chief Executive Officer of RMMCH and the Heads of the Department of Dentistry and Anaesthesiology of RMMCH will be approached for consent to conduct research in the hospital and in the respective departments (Appendix A).

Informed consent will be obtained from the caregiver of the child presenting for surgery. The caregiver will be approached and invited to participate in the study. Those that agree will be given an information letter (Appendix B) and a consent form will be signed (Appendix C). Children from the age of 6 years will be asked to sign an assent form (47) (Appendix D).

Anonymity and confidentiality of the participants will be maintained. Anonymity will be maintained by allocating a study number to each patient and ensuring that the data collection sheet does not reveal any identifying information. A sheet with the patient's names and study number will be stored separately. Confidentiality will be ensured by allowing only the researcher, research assistant and supervisor's access to the raw data.

The study will assess the presence or absence of ED in the recovery room. If ED persists, the researcher will ensure that the patients are appropriately treated and only discharged once calm and pain-free and all the discharge criteria have been met.

Raw data will be securely stored for six years after the completion of the study.

The ethical principles of beneficence, autonomy and justice that govern research will be upheld in this study as outlined below (49). This study will be conducted in adherence to the principles of the Declaration of Helsinki (50) and the South African Guidelines for Good Clinical Practice (51).

5.8 Methodology

5.8.1   Research design
The research design forms the map of the study and determines the approach of the researcher to obtain sources of information, collect data and analyse and interpret results (52).

This is a prospective, descriptive, contextual study.

A prospective study measures outcomes at the time the study takes place in a specific population (52). ED will be documented in the group of patients presenting for dental surgery from September 2015 until data collection is complete.

A descriptive study is designed to provide a picture of a situation as it occurs naturally, i.e. the characteristics of the sample are defined without manipulation of variables (52). Demographics and assessment of risk factors will be collected from the participants without any intervention to prevent ED.

A contextual study is conducted in a specific population or group of people or in a specific location described by De Vos (53) as a "small-scale world". This study will measure the occurrence of ED in a specified subgroup of patients presenting for dental surgery at RMMCH.

5.8.2   Study population
This study will include children presenting to RMMCH for elective dental surgery under general anaesthesia.

5.8.3   Study sample
5.8.3.1   Sample size
The sample size was determined in consultation with a biostatistician. A sample size of 85 was calculated to achieve a 95% confidence interval (2-tailed) and a power of 80%. This was based on a minimum expected occurrence of 20% of ED in the population. Thus 17 out of 85 patients should have ED in the sample.

5.8.3.2   Sample method
Sampling is intended to predict outcomes or trends that can be extrapolated to a larger population (54). In this study consecutive, convenience sampling will be used.

Convenience sampling is described as non-random sampling of the most easily accessible individuals in the sample population. Consecutive sampling attempts to include all available

individuals in the accessible population. Consecutive sample is the best form of convenience sampling (54).

5.8.3.3 Inclusion and exclusion criteria

The inclusion criteria of this study will be:

- patients between the ages of two to six years.
- ASA I or II patients.
- scheduled for dental surgery under general anaesthesia.

The exclusion criteria of this study will be:

- refusal of consent by the caregiver.
- mental retardation and developmental delay.
- contraindication or allergy to sevoflurane or other study drugs.
- caregiver unable to converse in English.

5.8.4 Collection of data

5.8.4.1 Data collection sheet

A data collection sheet (Appendix E) will be completed for each study participant. An extensive review of the literature was used to compile the data collection sheet to ensure that all relevant personal details and risk factors are elucidated so that meaningful inferences can be drawn from the data.

The information will be divided into four sections as follows.

- Section 1 will document the patients personal details:
  - study number
  - date of birth
  - age
  - gender
  - ASA classification
  - history of traumatic medical experience
  - previous anaesthesic/dental procedures
  - preoperative medication
  - education level of the caregiver.

- Section 2 will document preoperative anxiety of the child using the mYPAS:
  - activity
  - vocalisations

- o emotional expressivity
- o state of apparent arousal
- o use of parents.

- Section 3 will document the intraoperative course:
  - o volatile used
  - o duration of anaesthesia
  - o duration of surgery
  - o number of teeth extracted, filled or other procedures done
  - o intraoperative medications
  - o complications and management thereof.

- Section 4 will document the postoperative course:
  - o time of arrival in recovery room
  - o extubation time
  - o state of arrival in recovery
  - o PAED score at five minute intervals for 30 minutes
  - o interventions
  - o start time of ED
  - o end time of ED
  - o duration of ED
  - o discharge time from the recovery room
  - o time in the recovery room.

5.8.4.2   Data collection process

Permission will be obtained from the relevant authorities to conduct this research. Data will be collected by the researcher. A trained research assistant will assist when the researcher is unable to collect data.

On the morning of the surgery, the researcher will approach the caregiver in the ward and invite participation in the study. The study will be explained and an information letter (Appendix B) will be given to those who agree to participate. The caregiver will be requested to sign consent (Appendix C). Children from the age of six years will be requested to sign assent (Appendix D).

Section one of the data collection sheet will be completed by the researcher with the assistance of the caregiver.

A trained research assistant will complete section two, the mYPAS, at the time of induction of anaesthesia in theatre. The researcher will also complete section three, the intraoperative course.

Each participant will receive a standardised anaesthetic procedure by the anaesthetist allocated to the dental list, described as follows. Premedication will not be given as it is not routinely prescribed for dental surgical procedures. The parent will accompany the child into the operating room. Standard monitors, i.e. non-invasive blood pressure, oxygen saturation probe and 3 lead ECG will be placed on the patient. An inhalational induction with sevoflurane and oxygen by mask will be performed. Once the child is asleep, the parent will be asked to leave the theatre and an intravenous line will be placed. Intravenous propofol will be given; the dose titrated to effect; to facilitate intubation. The airway will be secured with a nasal endotracheal tube and a throat pack will be placed. Ventilation will be controlled or supported as indicated to achieve normocapnia.

The dental surgeons will infiltrate the surgical area with lignocaine. Either intravenous paracetamol (15mg/kg) or a rectal suppository (paracetamol (30mg/kg) or non-steroidal anti-inflammatory drug (1mg/kg)) will be given intraoperatively. If for any reason, patients require additional medication or interventions intraoperatively; this will be documented and taken into account in the analysis of the results.

On completion of the surgery, the throat pack will be removed and the child will be transferred to the recovery room intubated or extubated as preferred by the anaesthetist. The child will be extubated once fully awake by the attending anaesthetist. Emergency ventilation, airway equipment and a functional anaesthetic machine are present in the recovery room in case of any emergencies.

The researcher will observe the patients in the recovery room and complete section four of the data collection sheet. If ED persists in the recovery room, the patient will be treated with intravenous fentanyl (1ug/kg) at the discretion of the researcher or trained research assistant and observed in the recovery room.

Children who exhibit excessive anxiety will be referred to the Psychology Department at RMMCH for emotional containment at the convenience of the parents during the available consultation times (Mrs. Elsabe Jordaan 011 470 9244).

5.8.5 Data analysis

Data will be captured on a Microsoft Excel® 2010 spreadsheet. The statistical program Statistica™ version 13, will be used to analyse the data, in consultation with a biostatistician. Descriptive and inferential statistics will be used to report the study findings. Categorical variables will be described using frequencies and percentages. Continuous variables will be reported using means and standard deviations or medians and inter-quartile ranges depending on the distribution of the data. Demographic and procedure-related variables will be compared with the development of ED using Chi^2 or Fishers Exact tests depending on the numbers in each group. The mYPAS score, age and duration of anaesthesia will be correlated with the highest PAED score achieved during the recovery period using either Pearson's or Spearman's rank correlation. State of arrival of patients in the recovery room and time to discharge from the recovery room with and without ED will be compared using either the Students t-test or the Mann-Whitney test. A p value of <0.05 will be considered statistically significant.

5.9 Significance of the study

Surgery has been described as a particularly difficult life experience for children and parents (40, 41). An association between perioperative anxiety and PMB, the earliest manifestation of which is ED in the recovery room, has been described in several studies (12, 14, 38, 40, 41). This spectrum of perioperative behavioural disturbances, from preoperative anxiety to ED and PMB, has been associated with adverse psychological and physiological outcomes in the patient as well as with parental dissatisfaction (11, 31, 38, 39).

The last decade has seen a surge in the literature around this subject (38, 55). Much effort has been made by international researchers to standardise the definition of ED, to validate the assessment tools used for the diagnosis and to investigate various methods of preventing the development of ED.

No South African studies could be identified that document the incidence, risk factors and long term outcomes associated with the development of ED. This study will provide insight into defining the incidence of ED, particularly in our patient population and will highlight risk factors so that preventative methods can be appropriately employed. It can further serve as a basis to direct further research in the field of paediatric anaesthesia.

5.10   Validity and reliability of the study

The validity of the study refers to the degree that the conclusions drawn from the study are justified. It refers to the ability of a data collection process to accurately measure what it should (56).

The reliability of the study refers to the consistency and reproducibility of the results obtained with a particular instrument; it indicates the degree of random error in the method of measurement (56, 57).
The validity and reliability of the study will be ensured in the following ways.

- An appropriate study design and data collection techniques will be employed.
- A representative sample size was determined with the help of a biostatistician.
- A standardised anaesthetic will be administered to all the patients to eliminate bias introduced by confounding variables. If the attending anaesthetist deems it necessary for additional treatment or intervention, this will be documented and taken into account in the final analysis.
- Data collection of the scoring systems will be done by the researcher and a trained research assistant to decrease inter-observer bias.
- Assessment of preoperative anxiety and ED are conducted with validated scales used in the literature. The threshold values for each will also be based on the validated values.
- Appropriate exclusion criteria will be applied to exclude patients that may skew the results.
- Every eighth entry on Microsoft Excel ® 2010 will be checked for accuracy.
- Data analysis will be done in consultation with a biostatistician.

5.11   Potential limitations of the study

Burns and Grove (57) define study limitations as problems with the study, either theoretical or methodological, that may limit the conclusions that can be made from the results.

The contextual nature of the study is a limitation. The study is limited to a single hospital. Therefore, the results of this study may not be generalisable to other populations. As the study examines ED after dental surgery only, the findings may not be generalisable to other surgical procedures.

Convenience sampling is also a limitation as all members of the population do not have an equal chance of being recruited (54). As consecutive, convenience sampling will be used; every child

on the dental list on the days of data collection will be included in the study provided they meet the inclusion criteria.

5.12 Project outline

	Oct 2014	Nov 2014	Jan 2015	April 2015	Sept-Febr 2016	Mar-Jun 2016	July-Sept 2016	Oct 2016
Chapter 1,2,3	■	■						
Protocol	■	■						
Ethics approval			■					
Postgrad approval				■				
Data collection					■			
Data Analysis						■		
Chapter 4 & 5							■	■
Submission								■

5.13 Financial plan

The Department of Anaesthesiology will bear the cost of printing and paper for the study.

Description	Price/item	Number of copies	Total
Paper	R1/page	1500	R1500
Binding	R150/copy	3	R 450
Total Cost			**R1950**

5.14 References

1.   Sikich N, Lerman J. Development and Psychometric Evaluation of the Pediatric Anesthesia Emergence Delirium Scale. Anesthesiology. 2004;100(5):1138-45.

2.   Da Silva L, Braz L, Modolo N. Emergence agitation in pediatric anesthesia: current features. J Pediatr (Rio J). 2008;84(2):107-13.

3.   Locatelli B, Ingelmo P, Sahillioglu E, Meroni V, Minardi C, Frawley G, et al. Emergence delirium in children: a comparison of sevoflurane and desflurane anesthesia using the Pediatric Anesthesia Emergence Delirium scale. Pediatr Anesth. 2013;23(4):301-8.

4.   Eckenhoff J, Kneale D, Dripps R. The incidence and etiology of postanesthesic excitement. A clinical survey. Anesthesiology. 1961;22(5):667-73.

5.   Vlajkovic G, Sindjelic R. Emergence delirium in children: many questions, few answers. Anesth Analg. 2007;104(1):84-91.

6.   Cole J, Murray D, McAllister J, Hirshberg G. Emergence behaviour in children: defining the incidence of excitement and agitation following anaesthesia. Paediatr Anaesth. 2002;12(5):442-7.

7.   Bong C, Ng A. Evaluation of emergence delirium in Asian children using the Paediatric Anaesthesia Emergence Delirium scale. Pediatr Anesth. 2009;6(19):593-600.

8.   Dahmani S, Delivet H, Hilly J. Emergence delirium in children: an update. Curr Opin Anesthesiol. 2014;27(3):309-15.

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Appendix A CEO/HOD letter

Dr Z Jooma

Department of Anaesthesiology

University of the Witwatersrand

zainub.jooma@gmail.com

3 November 2014

The Chief Medical Officer/Head of Department

I am a registrar in the Department of Anaesthesiology. I am currently conducting research for the completion of my Masters of Medicine in Anaesthesiology: Emergence delirium in children undergoing dental surgery under general anaesthesia. I hereby request permission to conduct research at Rahima Moosa Mother and Child Hospital.

The study will be conducted on children presenting for dental surgery under general anaesthesia. It will entail the measure of the incidence of emergence delirium and association of risk factors. The method of administering the anaesthesia will follow usual practice and patients will be treated as per routine for any complications. Emergence delirium will be managed appropriately in the recovery room if it is deemed necessary.

This study has received Ethics (M150104) and Postgraduate approval. It is a descriptive study and there will be no cost to the hospital.

The research will be conducted from April 2015 to July 2015; the length of time may be extended a further three months if an adequate number of patients have not been recruited.

Thanking you in advance for your assistance.

Sincerely

Dr Zainub Jooma

Registrar: Department of Anaesthesiology

Appendix B Participant Information letter

Emergence delirium in children undergoing dental surgery under general anaesthesia

Hello, my name is Zainub Jooma. I am studying at the University of the Witwatersrand to become an anaesthetist. An anaesthetist is a doctor who specialises in looking after patients while they are in theatre. We make sure that patients do not feel or remember anything during the operation and we give medication to take away the pain after the operation.

As part of my studies, I have to do a research study and I would like your child to take part. I want to find out how many children that go to theatre have "emergence delirium" after they wake up. Emergence delirium happens when the children wake up from the anaesthetic and feel confused, cry a lot and may scream. This happens commonly to children because of the medication we give them during the operation and it only lasts a short while.

If you agree to be part of the study, I will fill out a form with your child's age and other personal information. I will ask you a few questions about your child's behaviour at home. This will not take more than five minutes. You will go into theatre with your child and once your child is asleep you will wait outside. Once the operation is done, you will sit with your child in the recovery room. You may ask questions at any time if you are not certain about anything.

This study has been approved by the Human Research Ethics Committee (Medical) (number) and the Postgraduate Committee of the University of the Witwatersrand.

There is no harm in participating in the study. Your child will receive the normal anaesthetic and pain medication in theatre and when they come out of theatre.

By being part of this study, you can help us understand children's behaviour in theatre better so that we can give a better anaesthetic to make them as comfortable as possible.

If you do not want your child to be in the study, your child does not have to take part. It is your decision to take part in the study. The doctors and nurses will not be upset with you, and your child will receive exactly the same anaesthetic as children who will take part in the study. If you change your mind about being in the study, it will not be a problem if you withdraw.

For more information, you may call me on (011) 488-4397. You may also contact Professor Peter Cleaton-Jones, chair of the Human Research Ethics Committee, on (011) 717-1234.

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

Thank you very much for your time.

Regards
Zainub Jooma

Appendix C Consent to participate

CONSENT TO PARTICIPATE IN RESEARCH STUDY

Research title: Emergence delirium in children undergoing dental surgery under general anaesthesia

I _____, parent/caregiver of _____
understand what this study is about and give consent for my child/the child I care for to participate in
this study. I have read and understand the information sheet and my questions have been answered. I
am aware that the procedures will not harm the child in any way. 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.

_____

 Name of subject

_____

Signature of subject

_____

Date

_____

Name of researcher

_____

Signature of researcher

_____

Date

Appendix D Assent to participate

ASSENT TO PARTICIPATE IN RESEARCH STUDY

Research title: Emergence delirium in children undergoing dental surgery under general anaesthesia

I, _____, am happy 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 subject

_____

Signature of subject

_____

Date

_____

Name of researcher

_____

Signature of researcher

_____

Date

Appendix E Data collection sheet

Section 1: Personal details

Date

Study number

Date of Birth

Age   (months)

Gender | M | F |

ASA classification | 1 | 2 |

History traumatic medical encounter | Y | N |

Previous anaesthetic/dental procedure | Y | N |

Preoperative medication | Y | N |

If yes,
specify

Education level of caregiver | Primary | Secondary | Tertiary |

Section 2: The modified Yale Preoperative Anxiety Scale

Study No.

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=   X20=

Section 3: Intraoperative course   **Study   No.**

Volatile

Sevoflurane	Other

_____

Anaesthesia

Start time	
End time	

Duration

Surgery

Start time	
End time	

Duration

Number of teeth extracted/fillings/other

Intraoperative medication (Name/Dose)

Opioids	
NSAID	
Paracetamol	
Other	

Complication

Laryngospasm
Bronchospam
Allergic reaction
Other
None

Management

Section 4: Postoperative course   **Study No.** ☐

Arrival time in recovery ☐

Intubated	Extubated
Awake	Asleep

Extubation time ☐

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

5 minutes ☐ 20   10 minutes ☐ 20   15minutes ☐ 20

20minutes ☐ 20   25minutes ☐ 20   30 minutes ☐ 20

Interventions

None
Physical restraint
Consoled by parent
Medication

Medication
(if any)

☐

ED start ☐

ED end ☐

ED duration ☐

Discharge time ☐

Time in recovery ☐