EVALUATION OF STRESS RESPONSE AND ANXIETY SCORES OF PAEDIATRIC PATIENTS SEDATED WITH INTRANASAL DEXMEDETOMIDINE VS PLACEBO: A RANDOMIZED CONTROL TRIAL

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Many thanks from the bottom of my heart to my comrades, including anaesthesia and surgical-based doctors, who have helped me, especially in carrying out the study and patient recruitment, and the ward staff of 2 Selatan.

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My baby Aadhvik, I apologize for all the times I was not around to watch you grow up. But God willing we will be together soon.

Thank you.

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LIST OF SYMBOLS AND ABBREVIATIONS

ACTH	Adrenocorticotrophic Hormone
ADHD	Attention Deficit Hyperactive Disorder
ASA	American Society of Anaesthesiologist
ASD	Autism Spectrum Disorders
CI	Confidence Interval
DEX	Dexmedetomidine
ECG	Electrocardiography
ED	Emergence Delirium
EEG	Electroencephalogram
Etc.	etcetera
FLACC	Face, Legs, Activity, Crying, Consolability Scale
GOT	General Operating Theatre
HPA	Hypothalamic – Pituitary – Axis
HR	Heart Rate
HUSM	Hospital Universiti Sains Malaysia
JEPEM	Jawatan Kuasa Etika Penyelidikan Manusia
KGS	Kilograms
m-YPAS	modified Yale Preoperative Anxiety Scale
MAD	Mucosal Atomizer Device

MAP	Mean Arterial Pressure
Mcg/kg	Microgram per kilogram
Mg/kg	Milligram per kilogram
MIN	Minutes
MOE	Ministry of Higher Education
MOH	Ministry of Health
NS	0.9% Normal Saline
PD	Perioperative Dialogue
QMH	Queen Mary Hospital, Hong Kong
SBS	Sedation Behavior Score
SpO2	Pulse oximeter
UM	Universiti Malaya
VS	Versus
%	Percentage
<	less than
=	equals

APPENDICES

ABSTRAK

Penilaian tindak balas stress dan skor ketenangan dikalangan pesakit pediatrik yang ditenangkan dengan intranasal dexmedetomidine berbanding dengan placebo : kajian kawalan rawak

***Pengenalan**:* Kelebihan dexmedetomidine (DEX) sebagai ubat penenang dan penahan sakit yang dapat mengekalkan kestabilan kardiovaskular menjadikannya ubat yang ideal digunakan untuk populasi pediatrik. Ia merupakan ubat penenang pilihan untuk digunakan kerana ia lebih selamat dan kurang kesan sampingan dan kesan pengar pasca pembedahan. Tambahan pula, penggunaan ubat DEX yang diberikan secara intranasal sesuai dan mudah diberikan kepada pesakit pediatrik.

***Kaedah**:* Ini merupakan penyelidikan rawak yang terkawal dan prospektif. Sejumlah 60 pesakit pediatrik yang menjalani pembedahan elektif telah direkrut ke dalam kajian ini secara rawak untuk menerima ubat sama ada DEX (n = 30) atau 0.9% normal saline (NS, n = 30) secara intranasal. Hasil utama kajian adalah untuk mengukur tahap kortisol asas dalam serum dan tahap kortisol dalam serum pasca pemberian ubat bius. Hasil sekunder termasuk mengkaji skor *'Modified Yale Preoperative Anxiety Scale'*, *'Sedation Behaviour Scores' (SBSs)* dan kestabilan hemodinamik.

***Keputusan**:* Kedua – dua kumpulan NS dan DEX menunjukkan peningkatan yang ketara dalam paras kortisol dalam serum jika dibandingkan dengan paras dasar. Perbandingan antara kumpulan secara berpasangan tidak menunjukkan perbezaan yang signifikan dalam paras kortisol dalam serum (95% CI 1.73(-57.28, 60.75); p = 0.95). Kedua – dua kumpulan NS dan DEX menunjukkan peningkatan yang ketara dalam SBS pasca sedasi. Terdapat peningkatan yang signifikan dalam kadar denyutan jantung untuk kumpulan NS selepas menerima ubat bius. (95%CI – 10.23 (-15.57, -4.90) p = 0.00); tetapi kumpulan DEX tidak menunjukkan sebarang peningkatan yang signifikan (95%CI – 7.17 (-15.405, 1.07); p = 0.09).

***Kesimpulan**:* Pemberian ubat DEX secara intranasal pada dos 1mcg/kg dapat memberi tahap sedasi yang memuaskan untuk pesakit pediatrik. Akan tetapi, ia tidak dapat mengurangkan kesan tindak balas stres disebabkan oleh induksi bius.

Kata kunci: *Dexmedetomidine, bius umum, intranasal, pediatrik, skor penenang, tahap serum kortisol*

ABSTRACT

Evaluation of stress response and anxiety scores of paediatric patients sedated with intranasal dexmedetomidine vs placebo: A randomised control trial

Background: Dexmedetomidine's (DEX) favourable properties that include analgesia, sedation, and maintenance of cardiovascular stability renders it an ideal drug for paediatric patients. It provides a safer option with less concern for postoperative sedation and hangover effect. Furthermore, intranasal dexmedetomidine is tolerable and easily administered to paediatric patients.

Methods: This was a prospective randomized controlled trial. A total of 60 paediatric patients who underwent elective surgery were included in the study and randomly assigned to receive either intranasal DEX (n = 30) or intranasal 0.9% normal saline (NS, n= 30). Primary outcomes measured the baseline serum cortisol level and serum cortisol postinduction of anaesthesia. Secondary outcomes included Modified Yale Preoperative Anxiety Scale scores, Sedation Behavior Scores (SBSs) and haemodynamic stability.

Results: Both NS and DEX groups showed a significant increase in serum cortisol levels when compared with the baseline. Pairwise comparisons between the groups showed no significant difference in serum cortisol levels (95%CI 1.73(-57.28, 60.75); p = 0.95). Both NS and DEX groups showed significant improvement for SBS post sedation administration. There was a significant increase in post-induction of anaesthesia heart rate level in the NS group (95%CI – 10.23(-15.57, -4.90) p = 0.00); however, it was not significant in the DEX group (95% CI – 7.17(-15.405, 1.07); p = 0.09)

Conclusion: At a dose of 1 mcg/kg, intranasal DEX provides a satisfactory level of anaesthesia for paediatric patients; however, it does not reduce the stress response to induction of anaesthesia.

Keywords: *dexmedetomidine, general anaesthesia, intranasal, paediatric, sedation score, serum cortisol level*

CHAPTER 1: INTRODUCTION

Introduction

Dexmedetomidine is a more selective and potent alpha2-adrenergic agonist than clonidine. In the mammalian brain, both drugs exhibit a large range of actions, which include analgesia, sedation, anaesthetic-sparing, and being sympatholytic.[1,2] Besides the aforementioned properties, cellular signalling pathways that possess a role in neuroprotection have also been reported *in vitro* and *in vivo*.[1] in several studies conducted supporting its favorable properties and contributions in anaesthesia and intensive care. [3-6]

Dexmedetomidine has been described for use in paediatric populations for over a decade.[6] The use of dexmedetomidine has widened into the perioperative setting not only because of its favourable physiological properties but also due to its limited adverse effects.[6] Nonetheless, before administering dexmedetomidine in paediatric patients, its contraindications and biphasic effects on blood pressure need to be thoroughly understood.[7]

There are several adverse clinical outcomes associated with the incidence of perioperative anxiety in paediatric patients.[8] The common ones include an increased analgesic requirement, emergence delirium, and maladaptive behavioural changes, namely separation anxiety, enuresis, sleep disturbance, and eating disorders.[8-10] The hospitalization, surgery, and induction of anaesthesia carry a significant stressor for paediatric patients. [11-13]

Salivary cortisol level was found to be decreased with maternal presence during the induction of anaesthesia in paediatric patients.[14] The level was found to be significantly decreased during the induction of anesthesia and recovery, reflecting a

reduced stress response to anaesthetic induction with maternal presence.[15] Another study proved that perioperative dialogue intervention composed of caring, continuity, and ongoing conversation is associated with lower cortisol levels and even caused a reduction in the morphine requirement of paediatric patients between the age of 5 and 11 years. [16]

We conducted a single-centre prospective randomised controlled trial assessing the stress response and anxiety scores of paediatric patients who underwent elective surgeries. Baseline and post-induction of anesthesia serum cortisol levels were compared. Recruited patients were either sedated with intranasal dexmedetomidine or normal saline (placebo; NS). We hypothesized that post-induction of anesthesia serum cortisol levels of the intervention group will be reduced (intranasal DEX) compared with that of the placebo group.

Literature Review

In 2012, Yuen et al conducted a study involving subjects from Queen Mary Hospital Hong Kong (QMH) and University Hospital, Malaysia (UM). They compared 2 doses of intranasal dexmedetomidine 1mcg/kg and 2mcg/kg as perioperative sedation for various types of surgery from circumcision to orthopaedic surgery. 116 patients between the ages of 1 to 8 were included in their study. From the data collected, the conclusion made was that both of the doses produced satisfactory levels of sedation in a similar manner for the smaller children (1-4) years old (95%CI,0.5-2.7) whereas for children between the ages of 5-8 (95%CI,1.4-80.2) higher concentration of 2mcg/kg intranasal dexmedetomidine produced a higher level of satisfaction[5].

Yuen and a group of researchers from Queen Mary Hospital Hong Kong (QMH) conducted another study to determine the optimal timing for administration of dexmedetomidine as perioperative sedation in paediatric patients. It involved 100 patients randomized into 5 groups, A B C D and E. Intravenous cannulation was attempted by paediatric anaesthetists at different timings; 30, 45, 60 and 75 min for respective groups. Group E received intranasal placebo consisting of 0.9% Normal Saline and cannulation was attempted at 45 mins. The results showed that there was no significant difference between the 5 groups in terms of satisfactory sedation level. The median (95%CI) for onset of sedation was 25 (25-30) minutes whereas the duration of sedation was 85 (55-100) minutes[6].

In another related study, Aynur Akin et al from Erciyes University Turkey conducted a study comparing intranasal dexmedetomidine 1mcg/kg and intranasal midazolam 0.2mg/kg in paediatric patients undergoing adenotonsillectomy. A total of 90 children between the ages of 2-9 years old were enrolled in this study. They then

assessed the satisfaction scores on mask induction and separation from parents. From the data collected, they noticed that satisfaction scores upon introducing anaesthetic via face mask were higher in the midazolam group, 82% as compared to 60% in the dexmedetomidine group.

There was no significant difference during separation from parents between those 2 groups. They also noticed that the requirement of postoperative analgesia was higher in the midazolam group. The conclusion was made that midazolam was a superior sedative agent as compared to dexmedetomidine for the introduction of an anaesthetic face mask[7].

Markku et al from University of Finland conducted a study to evaluate the bioavailability of dexmedetomidine after an extravascular dose in a healthy subject. 2 mcg/kg dexmedetomidine was administered in several routes namely intravenous, intramuscular, buccal and oral. The oral and buccal drug concentration-time data was then analyzed using linear one-compartmental model; intravenous data using two-compartmental model and intramuscular data using a non-compartmental model. The results obtained showed that mean (95%CI) for oral route was 16%, the buccal route was 82% and intramuscular route was 104%. The conclusion made was that dexmedetomidine administered via buccal route was an effective method of drug administration[8].

Moreover, it is non-invasive and provides an alternative route to administer the drug. The study, however, did not specifically involve intranasal route and was conducted among healthy adult subjects. It gave us an idea that the intranasal route may produce high drug plasma concentration and although limited studies have been done on our target population, we predict that delivering dexmedetomidine via

intranasal route is as effective as delivering it via the buccal route as both are able to avoid first-pass metabolism.

In 2011, researchers from Skaraborg Hospital, Sweden were able to prove that perioperative dialogue intervention which composed of caring, continuity and ongoing conversation is associated with a lower level of cortisol and even caused a reduction in morphine requirement in paediatric patients. Their study involved children between the ages of 5-11 years and were randomly allocated into 3 groups; standard perioperative care, standard perioperative care with perioperative information and the perioperative dialogue (PD) group. Salivary cortisol level was taken pre and postoperatively. The PD group had a significantly lower level of cortisol ($p<0.01$) and significantly lower consumption of morphine ($p=0.014$)[4].

Study Objectives

General Objectives

To evaluate the stress response and anxiety scores in paediatric patients sedated with intranasal dexmedetomidine when undergoing general anesthesia for elective surgery in Hospital Universiti Sains Malaysia (HUSM).

Specific Objectives

- To compare mean serum cortisol level preoperatively and post-induction in paediatric patients sedated with intranasal dexmedetomidine vs placebo.
- To compare mean anxiety levels by using modified Yale Preoperative Anxiety Scales (m-YPAS) pre-and post-induction of general anaesthesia in paediatric patients sedated with intranasal dexmedetomidine vs placebo.
- To determine the proportion of the safety profile via haemodynamic monitoring in paediatric patients sedated with intranasal dexmedetomidine vs placebo.
- To compare mean total analgesic requirement in paediatric patients sedated with intranasal dexmedetomidine vs placebo.

Null Hypothesis

- Intranasal dexmedetomidine delivered to paediatric patients is a superior sedative agent, safe for children and capable of reducing anxiety levels.
- Intranasal dexmedetomidine will reduce postoperative pain and reduce serum cortisol level post-induction of anaesthesia as compared to placebo.

CHAPTER 2: STUDY PROTOCOL

Research Methods and Methodology

Research Design

Double-blinded prospective randomized controlled trial (Patient and final assessor)

Study Period

6 months (February 2021 – July 2021)

Study Population

Paediatric patients undergoing elective surgery of various specialties in Hospital Universiti Sains Malaysia who do not have any contraindications as mentioned in the exclusion criteria. Patients were screened and recruited preoperatively by the anaesthetist running the list one day preoperatively.

Study Area

Hospital Universiti Sains Malaysia (HUSM) involving the following areas:

- Paediatric Ward (2 Selatan)
- General Operating Theater (GOT) – including reception and recovery area

Subject Criteria

Inclusion Criteria

- Paediatric patients age 1-12 years old
- Weight of patient between 10 – 60 kgs
- American Society of Anesthesiologist (ASA) I or II
- Scheduled for elective surgeries
- Caregivers able to understand and provide informed consent

Exclusion Criteria

- Allergy to study drugs (dexmedetomidine, morphine, paracetamol etc.)
- Special need Children (Cerebral palsy, down syndrome, ADHD, ASD)
- Serious cardiac/respiratory diseases.
- Children with neuromuscular disorders or neurological diseases (epilepsy etc.)
- Children with Metabolic disorders
- Difficult airway cases
- Children on any kind of steroid therapy / HPA diseases
- Children with extreme anxiety mandating preoperative sedation
- Children requiring ventilatory support postoperatively

Sample Size Estimation

We planned a study of the continuous response of sedation score, anxiety scores, serum cortisol levels and haemodynamic profiles from independent control and experimental subjects with 1 control(s) per experimental subject.

To fulfil objective 1 and 2, based on previous studies we used repeated ANOVA tests using G-power and determined that with a power of study of 80%, we would require 16 patients per group. Using similar tests, between groups we would require 20 patients per group and within – between groups we would require 17 patients per group.

To fulfil objective 4, based on two mean formulas for an independent sample using G-power, with a power of study of 80% we would require 26 patients per group.

Considering the 10% dropout rate, the sample size required is 30 subjects for intervention and 30 subjects for control group, which totals 60 subjects.

Sampling Method

Block randomization was applied to randomize the participants into 2 groups to either receive intranasal dexmedetomidine at a dose of 1mcg/kg (Interventional) or intranasal 0.9% Sodium Chloride in equal volumes (Control). Convenience sampling was applied based on the surgery list obtained each day during the period of the study. Each patient was assigned to a randomized group and this information was blinded to the assessor (anaesthetist running the list) and the patient.

Subject Recruitment

Patients were assessed for eligibility for recruitment into this study based on the inclusion criteria. They underwent a thorough pre-anaesthetic evaluation, including detailed airway assessment, clinical history, general and systemic examination. Patients who fit into the exclusion criteria were deemed unfit to participate in this study. Both anaesthetic and study consent were taken from the parent/caregiver one day before a scheduled surgery.

Research Tools

We used Mucosal Atomizer Device (MAD) to administer the intranasal sedation. Standard monitoring devices such as non–invasive blood pressure, pulse oximetry (SpO2) and heart rate monitoring via electrocardiography (ECG) was used to record patient data whilst ensuring continued safety throughout the procedure. Specific sedation and anxiety scales, namely Modified Yale Preoperative Anxiety Score (my-PAS) and Sedation behaviour scores were used for additional assessment and data collection. Blood samples were also obtained preoperatively and post-induction of anaesthesia for the assessment of

serum cortisol. All data were recorded in a specific data collection sheet which was kept secured and confidential.

Operational Definitions

Modified Yale Preoperative Anxiety Scale

Table 1: Modified Yale Preoperative Anxiety Scale

Domain: Activity

1. Looking around, curious, playing with toys, reading (or other age-appropriate behaviour); moves around holding room/treatment area to get toys or go to parent; may move toward OR equipment
2. Not exploring or playing, may look down, may fidget with hands or suck thumb (blanket); may sit close to parent while waiting, or play has a definite manic quality
3. Moving from toy to parent in an unfocused manner, non-activity-derived-movements, frenetic/frenzied movement or play; squirming, moving on table, may push mask away
4. Actively trying to get away, pushes with feet and arms, may move the whole body; in the waiting room, running around unfocused, not looking at toys or will not separate from the parent

Domain: Vocalizations

1. Reading (nonvocalizing appropriate to activity), asking questions, making comments, babbling, laughing, readily answers questions but maybe 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 maybe screaming “no”
6. Crying, screaming loudly, sustained (audible through a mask)

Domain: Emotional Expressivity

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

Domain: State of Apparent Arousal

1. Alert looks around occasionally, notices/watches anesthesiologist (could be relaxed)
2. Withdrawn child sitting still and quiet, maybe sucking on thumb or face turned in to adult
3. Vigilant looking quickly all around, may startle to sounds, eyes wide, body tense
4. Panicked whimpering, maybe crying or pushing others away, turns away

The Modified Yale Preoperative Anxiety scale (m-YPAS) is an established and recognized tool for the assessment of pediatric anxiety levels preoperatively. It is an observational

checklist each consisting of four to six distinct behavioural descriptions. Four categories of behaviour are assessed: activity, vocalizations, emotional expressivity, and state of apparent arousal. Partial weights are used to calculate a total score ranging from 23 (low anxiety) to 100 (high anxiety).

Sedation Behavior Scores

Table 2: Sedation Behavior Scores

Sedation Score

1. Alert, awake
2. Drowsy, sleepy, lethargic
3. Asleep but responds to mild prodding or shaking
4. Asleep and does not respond to mild prodding or shaking

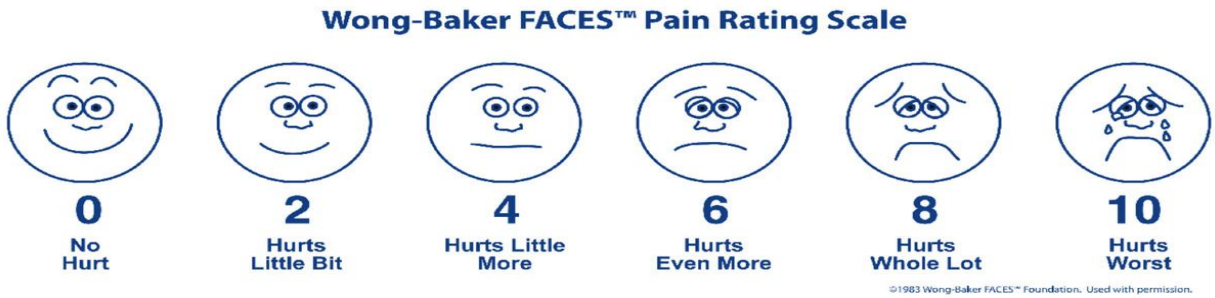
Behaviour Scores

1. Crying or resisting
2. Anxious and not reassurable
3. Anxious but reassurable
4. Calm and cooperative

Sedation and behaviour score is a simplified scoring system that is based on observational charting. It comprises 2 domains ranging from alert, awake, crying and resisting to asleep and not responding to mild prodding or shaking while being calm and cooperative. Higher scores indicate a higher level of sedation and are more favourable.

Wong-Baker Faces scale

Figure 1: Wong-Baker Faces scale



Wong-Baker Faces scale is a tool created with children to help them communicate their pain. Now the scale is used around the world with people ages 3 and older, facilitating communication and improving assessment so pain management can be addressed accordingly. There are 6 faces with each face representing a person who has no pain (hurt), or some, or a lot of pain. The patient chooses the face that best depicts the pain they are experiencing.

The FLACC scale

Table 3: The FLACC scale

	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tensed	Kicking or legs were drawn up
Activity	Lying quietly, normal position moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No crying (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractable	Difficult to console or comfort

The FLACC scale or Face, Legs, Activity, Cry, Consolability scale is a measurement used to assess pain for children between the ages of 2 months and 7 years or individuals that are unable to communicate their pain. It is an observational-based scale. The scale is scored in a range of 0–10 with 0 representing no pain. The scale has five criteria, which are each assigned a score of 0, 1 or 2. Higher scores indicate higher pain.

Data Collection Method

All perioperative data was collected by an investigator who is blinded to the patient's allocation.

Data was collected based on a designed data collection sheet.

The information recorded included:

- Baseline mean arterial pressure (MAP), heart rate (HR) and saturation of oxygen (SpO2)
- Baseline Modified Yale Preoperative Anxiety Scale (my-PAS) and My-PAS at 10 minutes post sedation
- Mean Arterial Pressure (MAP), Heart Rate and Sedation Behavior Scores before induction of anaesthesia
- Serum cortisol samples were also sent and recorded – baseline and postinduction of anaesthesia
- Total analgesic requirements including intraoperative and postoperative analgesia
- Postoperative data included pain scores as assessed by either Wong-Baker Faces pain rating scale or FLACC scores for smaller children. Additionally, sedation behaviour scores were also recorded.

Proposed Data Analysis

The data were recorded using Microsoft Excel and analysed using the IBM SPSS Statistics for Windows Version 21.0. The data cleaning process was initiated to minimize any errors that might skew the results. Numerical and categorical data were presented descriptively. The findings were analysed based on the types of data and their distribution. Categorical Data, were presented as frequencies and percentages. Numerical data were presented as means and standard deviations if normally distributed, and if not, as medians

and interquartile ranges. Numerical data of two independent groups were analysed using an independent T-test if the data is normally distributed, otherwise, the Mann Whitney test was used instead. All probability values are two-sided, and a level of significance of less than 0.05 (p-value < 0.05) were considered statistically significant.

GANTT Chart

Table 4: Projected Chronological Progress of Prospective Randomized Control Trial

Year	2020												2021											
Month	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
Topic Selection																								
Literature Review																								
Proposal Design and Presentation																								
Ethics Committee Review, Presentation and Corrections																								
Patient Recruitment and Data Collection																								
Data Interpretation and Statistical Analysis																								
Results and Discussion																								
Manuscript Preparation																								
Dissertation Presentation																								
Manuscript Submission																								
Publication																								

Study Flow Chart

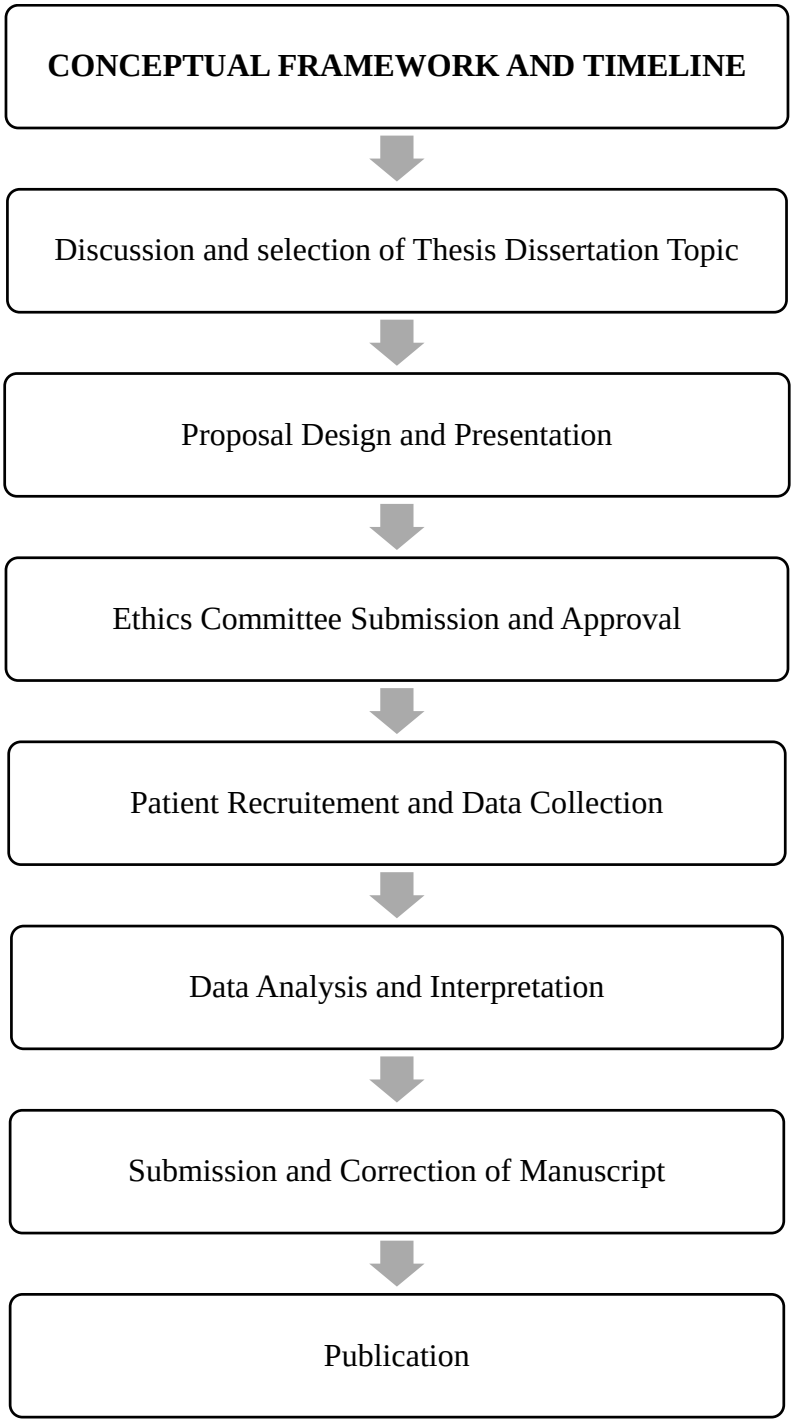


Figure 2: Study Flowchart

Ethical Consideration

Vulnerability

This study was commenced only after a full review and authorization from the ethics review panel of the Jawatankuasa Etika Penyelidikan Manusia USM (JEPEM). Patients enrolled in this study were subjected to the risks of conventional general anaesthesia regardless of the choice of preoperative sedation administered. The principal investigator and another anaesthesiology medical officer both attended to the patient during induction. The anaesthesiology medical officer in charge continuously monitored the patient throughout the surgery and during awakening (as per usual for any patient under general anaesthesia).

The second ethical consideration accounted for was the analgesic requirement during the intraoperative and postoperative periods. To accommodate this, the patients were administered analgesics as deemed required with no deviation from standard practice.

Information regarding the study and informed consent including management of complications was thoroughly explained to the patient's relative/caregiver before obtaining consent.

Declaration of conflict of interest

All investigators conducting this study are practising as anaesthesiology medical officers and specialists under the Ministry of Higher Education (MOHE) and Ministry of Health (MOH) and are not affiliated with any third party that may influence the outcome of this study. Neither the patient nor the principal investigators received any form of

reimbursement or incentives from the mucosal atomizer device (MAD) or Dexmedetomidine company.

Privacy and Confidentiality

No personal identifiers were collected. All subjects' information obtained in this study was kept and handled confidentially by applicable laws and regulations and maintained throughout the study and only used for the study. Subjects were not given access to personal information or study data. The study results were presented as grouped data and no individual responders were identified. All medical records and study data was stored and archived accordingly.

Ethical Approval

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)

Human Research Ethics Committee USM (HREC)

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JEPeM Code : USM/JEPeM/20090498
Protocol Title : Evaluating Stress Response and Anxiety Scores in Paediatric Patients Sedated with Intranasal Dexmedetomidine.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/20090498**, which should be used for all communications to JEPeM-USM in relation to this study. This ethical approval is valid from **10th February 2021** until **9th February 2022.**

Study Site: Hospital Universiti Sains Malaysia.

The following researchers are also involved in this study:

1. Dr. Huda Zainal Abidin
2. Dr. Praveena Seevaunnamtum

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical documents were included in the review on which this approval was based:

1. Parental Information Sheet and Consent Form (English version)
2. Parental Information Sheet and Consent Form (Malay version)
3. Data Collection Form
4. Modified Yale Preoperative Anxiety Scale
5. Pain Measurement Scale

The list of JEPeM-USM members present during the full board meeting reviewing your protocol is attached.

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2019: Continuing Review Application Form.**
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**

JEPeM
JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2019: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2019.**
6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2019: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

Sincerely,

ASSOC. PROF. DR. AZLAN HUSIN
Deputy Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)

Human Research Ethics Committee USM (HREC)

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Date of meeting : 16th December 2020
Venue : Through WEBEX Application
Time : 9.00 a.m – 2.30 p.m
Meeting No : 488

Members of Committee of the Jawatankuasa Etika Penyelidikan (Manusia), JEPeM Universiti Sains Malaysia who reviewed the protocol/documents are as follows:

Member (Title and Name)		Occupation (Designation)	Male/ Female (M/F)	Tick (✔) if present when above items, were reviewed
Deputy Chairperson: Associate Professor Dr. Azlan Husin		Deputy Chairperson of Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM	M	✔ (Deputy Chairperson)
Deputy Chairperson: Associate Professor Dr. Haslina Taib		Deputy Chairperson of Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM	F	✔ (Deputy Chairperson)
Deputy Chairperson: Professor Dr. Narazah Mohd Yusoff		Deputy Chairperson of Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM	F	✔ (Deputy Chairperson)
Secretary: Mr. Mohd Bazlan Hafidz Mukrim		Science Officer	M	✔
Members :				
1.	Dr. Azlina Yusuf	Lecturer, School of Health Sciences	F	✔
2.	Dr. Chandran Nadarajan	Lecturer, School of Medical Sciences	M	✔
3.	Assoc. Prof. Dr. Garry Kuan Pei Ern	Lecturer, School of Health Sciences	M	✔
4.	Prof. Dr. Irfan Mohamad	Lecturer, School of Medical Sciences	M	✔
5.	Mr. Khairul Ithma Mahdi	Assistant Registry, School of Health Sciences	M	✔
6.	Assoc. Prof. Dr. Mohd Hashairi Fauzi	Lecturer, School of Medical Sciences	M	✔
7.	Prof. Dr. Mohtar Ibrahim	Lecturer, School of Medical Sciences	M	✔
8.	Prof. Dr. Nik Hazlina Nik Hussain	Lecturer, School of Medical Sciences	F	✔
9.	Assoc. Prof. Dr. Saedah Ali	Lecturer, School of Medical Sciences	F	✔
10.	Assoc. Prof. Dr. Sarimah Abdullah	Lecturer, School of Medical Sciences	F	✔
11.	Dr. Surianti Sukeri	Lecturer, School of Medical Sciences	F	✔
12.	Assoc. Prof. Dr. Wong Kah Keng	Lecturer, School of Medical Sciences	M	✔
13.	Mrs. Zawiah Abu Bakar	Community Representatives	F	✔

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