Ketofol Versus Dexmedetomidine For Prevention Of Emergence Delirium In Pediatric Patients Undergoing Squint Surgeries: A Randomized Controlled Study.

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Table of Contents

Title Page 2
Study Title 2
Investigators 2
Introduction: 3
Aim of the work 4
Objectives: 4
Hypothesis 5
Ethical Considerations 5
Methodology 6-9
I. Study design 6
II. Study setting and location 6
III. Study population 6
IV. Eligibility Criteria 6
1. Inclusion criteria 6
2. Exclusion criteria 6
V. Study Procedures 6-8
1. Randomization (in RCT only) 6
2. Study Protocol 7,8
VI. Study outcomes 9
1. Primary outcome 9
2. Secondary outcome(s) 9
Statistical Analysis 9,10
I. Sample size 9
II. Statistical analysis 10
References 11,12

Title Page

Study Title

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Introduction :

Emergence delirium (ED) is a common postoperative complication in pediatrics characterized by disorientation, confusion, alterations in perception such as hypersensitivity to stimuli, inconsolable crying and moaning(1,2,3). The incidence of ED among pediatric population ranges from 25% to 80%, with high frequency in preschool children aging between 2- 6 years old (1,2,3). There are many risk factors contributing to ED including : patient age, preoperative anxiety, inadequate adaptive behavior, separation from parents, anesthetic drugs side effects, sudden arousal in unfamiliar enivronment and type of surgical operation including ophthalmological operations(strabismus surgeries)(3,4).

Emergence delirium appeared to be accompanied by unpreferable consequences as the child may remove intravenous devices, urinary catheter and surgical drain and may cause injury to surgical site. Child with ED need more care and delayed discharge from PACU(1,2). Accordingly, prevention of such complication is mandatory. To achieve this goal, Administration of adjunctive anesthetic agents including propofol, benzodiazepines, opioids, gabapentin, ketamine, clonidine, or dexmedetomidine may help in reducing the risk of emergence delirium in pediatric patients (5-7). Dexmedetomidine is a selective α2 receptor agonist known to have potent analgesic, sedative and anxiolytic effect, mainly due to binding to and stimulation of α2 receptors in the brain preventing activation of sympathetic system. Furthermore, it activates the same receptors in the dorsal horn of spinal cord leading to substance b release that have strong analgesic action (8,9). On the other hand, Ketamine is a noncompetitive antagonist of the N-methyl-D-aspartic acid (NMDA) receptor that have dose dependent hypnotic, analgesic and amnesic effects(10). However, being a

low-cost drug, ketamine has undesirable side effects like postoperative nausea, vomiting, laryngospasm, and desaturation (11).

Propofol is an anesthetic agent, with hypnotic and sedative effects of rapid onset short duration that allows rapid recovery, utilized for induction and maintenance of general anesthesia. Many studies demonstrated that propofol administrations for maintenance of anesthesia remarkably reduces incidence of ED (12). Considering that there is a synergistic clinical action between propofol and ketamine (ketofol) which has been used to prevent ED. Therefore, their doses decrease and undesirable side effects are reduced (13).

Despite many previous studies investigated effectiveness of adjunctive anesthetic agents in prevention of ED, there is lack of studies that focused on comparison between the efficacy of Dexmedetomidine and Ketefol in decreasing incidince of ED in preschool pediatric population undergoing eye surgeries , a previous study conducted a clinical trial on dexmedetomidine versus ketofol when given as a single bolus dose 10 minutes before the end of suregery in pediatric patients aged from 3 to 6 years old who underwent orthopedic surgeries under sevoflurane based General anesthesia(14), another one compared Dexmedetomidine versus Ketofol as a single bolus dose given 10 minutes before the end of surgery in pediatric population aged from 3 to 10 years old underwent oropharyngeal and urological operations(15) .

In this randomized controlled study, we will compare between efficacy of Dexmedetomidine vesus Ketofol for prevention of ED used as continous infusion through operation in pediatric patients aging from 2 to 6 years old undergoing squint surgeries .

Aim of the work

The aim of the study is to compare the effectiveness of ketofol for the prevention of emergence delirium in pediatric patients undergoing squint surgery, in comparison to dexmedetomidine.

Objectives :

- To compare the incidence of ED between children who received ketofol with those who received dexmedetomidine.
- To compare the adverse effect profile associated with both drugs regarding the effect on heart rate, mean arterial pressure, recovery time, nausea, and vomiting.

Hypothesis

We hypothesize that Ketofol, due to the combined effect of ketamine and propofol will be as effective as dexmedetomidine in preventing ED in pediatric patients undergoing squint surgery.

Ethical Considerations

The study protocol will be implemented after the approval by the Institutional Research Ethics Committee and then written informed consent will be obtained from all patients before enrollment into the study.

Methodology

I. Study design

A prospective randomized controlled double blinded study.

II. Study setting and location

The study will be conducted at the Specialized Children Hospital (Abo El-Rish), Cairo University.

III. Study population

All pediatric patients aged 2 to 6 years with ASA physical status I and II scheduled for squint surgery will be included in the study.

IV. Eligibility Criteria

1. Inclusion criteria

- All pediatric patients aged 2 to 6 years.
- Both sexes.
- ASA physical status I and II.
- Patients undergoing squint surgery.

2. Exclusion criteria

- Refusal of parents.
- Patient sensitivity to any of the study medications.
- Known neurological disease that can affect the assessment of ED postoperatively.

V. Study Procedures

1. Randomization (in RCT only)

A computer-generated sequence will be used for randomization and opaque envelopes will be used for concealment.

The investigator is the anesthesiologist who will prepare all the syringes with the study drugs and will prepare them in wrapped aluminum foils and sealed opaque envelope technique. which will be provided to another investigator just before administering them to the children. Monitoring and data collection will be done by a resident who is unaware of the study drugs and allocation.

Study Protocol

All patients meeting the inclusion criteria will be assessed for adequate fasting (except for oral clear liquids intake 2 hours before surgery, all children will fast for 6 hours.). Patients will attend in the preparation room one hour before the operation to get a preoperative checkup, as well as their age and body weight will be recorded. Premedicated by intramuscular injection of atropine 0.02 mg/Kg and midazolam 0.2 mg/Kg. On arriving the operating room, standard monitors including SpO2, ECG, and noninvasive blood pressure ((Dräger infinity vista XL). will be applied. Inhalational induction using Sevoflurane 5% will be performed, and after the loss of consciousness intravenous cannula will be inserted. Atropine 0.01 mg/kg will be administered, and appropriate sized endotracheal tube will be inserted after muscle relaxation using atracurium 0.5 mg/kg. Maintenance of anesthesia using 2% Sevoflurane in 50% O2 will be started, and its dose will be adjusted according to the measured pulse and mean arterial pressure (MAP), which was kept within 20% of their basal values, with the goal of keeping the BIS measurement between (40-60) and atracurium top-ups of 0.1mg/kg was given every 30 minutes for neuromuscular blockade. and controlled ventilation will be applied, aiming for EtCO2 to be between 32-34 mmHg. using (G.E-Datex-Ohmeda, Avance CS2, USA) anesthesia machine. Then patients will be randomized to either group A or group B.

Group A:

Five minutes after securing the airway, dexmedetomidine infusion will be started at a rate of 0.2 mcg/kg/hr.

Group B:

Five minutes after induction; Ketofol (ketamine to propofol ratio 1:4) will be infused at a rate of 0.6 ml/kg/hr. Ketofol will be prepared by adding 40 mg of ketamine to 160 mg of propofol and diluted to 20 ml with normal saline 0.9%.

The hemodynamic data, including heart rate and arterial pressure, will be documented every five minutes and any intraoperative complications including bradycardia, hypotension will be managed and documented. Ten minutes before the conclusion of the surgery the infusion in both groups will be stopped. All patients will receive 15mg/kg paracetamol IV.

After finishing the surgical procedure, sevoflurane will be discontinued, and the neuromuscular block will be reversed via neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg). The patient will be extubated when he/she is fully awake, expressing eye-opening and purposeful movement, in addition to maintaining good tidal volume. Then, the patients will be transferred to the PACU, where they receive O2 via a face mask to maintain oxygen saturation above 95%.

During their stay at PACU, delirium will be assessed at 5, 10, 15, 20, 25, and 30 minutes following extubation via the Pediatric Anesthesia Emergence Delirium scale (PAED) (Table 1), and ED will be established when the child have a score of 10 or more. If the child has a score of 10 or more, rescue sedation will be done via propofol 1 mg/kg. (14,17)

The postoperative pain will be assessed via the Face, Legs, Activity, Cry, and Consolability (FLACC) scale 0 = Relaxed and comfortable,1–3 = Mild discomfort, 4–6 = Moderate pain, 7–10 = Severe discomfort/pain. IV Fentanyl (1 µgm /kg) will be administered if the child expressed a score of 3 or more. (16)

Criteria	Not at all	Just a little	Quite a bit	Very much	Extremely	Score
The child makes eye contact with the caregiver/parent.	4	3	2	1	0	
The child's actions are purposeful.	4	3	2	1	0	
The child is aware of his/her surrounding.	4	3	2	1	0	
The child is restless.	0	1	2	3	4	
The child is inconsolable.	0	1	2	3	4	
Total score.						

Table 1. Pediatric Anesthesia Emergence Delirium (PAED) Scale Score. The PAED scale consists of 5 criteria that are scored using a 5-point scale. The scores of each criterion are added to make a total score. The maximum achievable score is 20. A score of ≥10 has 64% sensitivity and 86% specificity for the diagnosis of ED. A score of >12 100% sensitivity and 94.5% specificity for the diagnosis of ED (17).

Both pulse and MAP will be recorded at PACU on arrival, then at 5 and 10 minutes, then every 10 minutes until the discharge.

Any postoperative complications including bradycardia, hypotension or hypersensitivity reaction will be recorded. The incidence of postoperative vomiting, together with the duration of stay in PACU will be recorded.

Children were monitored in the PACU for all the above parameters until discharge and criteria of discharge are :
1. Fully awake
2. Calm
3. Stable hemodynamics
4. PAED scale < 10
5. Oxygen saturation > 92% on room air.

VI. Study outcomes

1. Primary outcome

The incidence of postoperative ED using PAED scale at time of admission to PACU in both groups.

2. Secondary outcome(s)

- Intraoperative vital signs So2 (%), HR (bpm) and MAP (mmhg) on admission to OR and every 5 minutes intraoperative.
- Incidence of Intraoperative complications (bradycardia and hypotension)
- PAED scale at 5, 10, 15, 20, 25 and 30 minutes after extubation.
- Total dose of rescue sedation by propofol (mg) at PACU.
- FLACC scale at PACU.
- Total dose of rescue analgesia (mic).
- Postoperative hemodynamics So2 (%), HR (bpm) and MAP (mmhg) after 5 and 10 minutes after admission to PACU then every 10 minutes till discharge.
- Incidence of postoperative nausea and vomiting.

- Length of stay in the PACU (minutes).

Statistical Analysis

I. Sample size

Sample size was calculated using G*Power version 3.1.9.2 (Kiel University, Kiel, Germany) software; based on our primary outcome ED could occur in dexmedetomidine group and ketofol group with PAED score 1.55±2.195, and 4.70±3.988 respectively (8); a total sample of 46 patients (23 in each group) were required to achieve a power (1–β) of 90%, and type I α error of 0.05. Six patients were added to compensate for any drop out. Thus, the final sample was 26 patients in each group; with total 52 patients.

II. Statistical analysis

All collected data will be revised for completeness and accuracy. Pre coded data will be entered on the computer using the statistical package of social science software program, version 26 (SPSS) to be statistically analyzed. Data will be summarized using: Mean and SD for quantitative variables and Number and percent for qualitative variable.

Comparison between qualitative variables will be done using chi square test. While independent T test for quantitative variable which will be normally distributed and non-parametric Mann-Whitney tests for quantitative variables which will be not normally distributed. One-way Anova will be used to compare quantitative variables between more than two categories for quantitative variable which will be normally distributed and nonparametric Kruskal-Wallis tests for quantitative variables which will not be normally distributed. Pearson or Spearman Correlation will be performed to explore correlations between the continuous variables. P value <0.05 will be considered significant.

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