

Bolus Doses of Ketofol versus Dexmedetomidine for the Prevention of Emergence Agitation in Children: A Prospective Randomized Controlled Clinical Trial

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Abstract

Background: Emergency agitation in children is a common problem with sevoflurane anesthesia which includes phenomena such as crying, excitation, agitation, delirium, and behavioral disturbances during early emergence from general anesthesia.

Materials and Methods: After the institutional ethics committee approval and written informed consent, 75 children aged 3-10 years, belonging to ASA I and II posted for oropharyngeal and urological surgeries, were randomly allocated for this randomized controlled study. Children were randomly assigned into three groups of 25 each into NS (control), KF (ketofol, k-0.25 mg/kg, p-1 mg/kg), and D (dexmedetomidine 0.3 ug/kg) groups. All the study drugs were administered 10 min before the end of surgery in the respective groups. In the post-anesthetic care unit (PACU), all children were evaluated for emergence agitation with modified objective pain scale (MOPS) and pediatric anesthesia emergency delirium scale (PAED) scores at 0, 10, 20, and 30 min, respectively. Hemodynamics and other side effects were monitored in the PACU. When all the children satisfied discharge criteria, they were shifted to the ward.

Results: The incidence and severity of emergence delirium were significantly high in the control group when compared to ketofol and dexmedetomidine groups according to MOPS and PAED scores at 0, 10, 20, and 30 min time intervals at PACU. Emergence agitation reduction was comparable between ketofol and dexmedetomidine groups, the difference being that in dexmedetomidine group, all the children satisfied discharge criteria earlier than ketofol group, and they appeared to be calm and cooperative while children of ketofol group were mildly restless. However, the difference between KF and D groups was not statistically significant.

Conclusion: Dexmedetomidine and ketofol caused a significant reduction in the incidence and severity of emergence agitation when compared to control group. Ketofol was as effective as dexmedetomidine in the prevention of emergence agitation when administered before the end of surgery, but children administered dexmedetomidine were calm and satisfied discharge criteria earlier than ketofol.

Key words: Dexmedetomidine, Emergence agitation, Emergence delirium, Ketamine, Propofol, Ketofol

INTRODUCTION

Emergency agitation in children is a common problem with sevoflurane anesthesia which includes phenomena

such as crying, excitation, agitation, delirium, and behavioral disturbances during early emergence from general anesthesia.¹ This phenomenon must be prevented by providing smooth emergence to pediatric patients. Otherwise, an irritable, uncooperative, inconsolable, and crying child with excessive motor activity may pose a significant problem to the parents and nursing personal to control and children may also harm themselves.²

High incidence of emergency agitation has given way to researchers to come up with numerous studies evaluating the incidence and severity of emergence agitation

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with inhalational and intravenous anesthetic agents.^{3,4} Parental presence at emergence, physical restraints, or pharmacologic interventions are the methods used to prevent emergence agitation. Various studies proved that medications such as fentanyl, ketamine propofol, ketofol, dexmedetomidine, clonidine, and midazolam have been used with differing efficacies of individual agents.^{5,6} This study aims to compare the efficacy of dexmedetomidine versus ketofol for the prevention of emergence agitation in children under sevoflurane-based anesthesia.

MATERIALS AND METHODS

After the institutional ethics committee approval and written informed consent, children aged between 3 and 10 years belonging to ASA Grade I and II were randomly selected for this prospective, randomized, controlled, and double-blinded study which was conducted in a tertiary care hospital from June 2016 to December 2016.

Inclusion Criteria

Male and female gender and children aged between 3 and 10 years belonging to ASA: I and II surgeries: Oropharyngeal and urological procedures were included in the study.

Exclusion Criteria

- Uncooperative children
- Children with neuropsychiatric disorders
- Children with chronic sedative medication
- Children with difficult airway
- Children with mental retardation
- Children with BMI > 18.5kg/m².

Children were randomly divided into three groups of 25 each using computer-generated random number table.

- Group NS: Were assigned to 10 cc of normal saline, 10 min before the end of surgery.
- Group KF: Were assigned to receive a combination of ketamine 0.25 mg/kg and propofol 1 mg/kg (ketofol) in a single syringe, the total volume made up to 10 ml.
- Group D: Were assigned to receive 0.3 ug/kg of dexmedetomidine, the total volume made up to 10 ml to ensure blinding.

All the children were premedicated with oral midazolam 0.25 mg/kg 25 min before surgery. Standard GA regimen was administered in all the children comprising of injection glycopyrrolate 20 ug/kg IV, ondansetron 0.1 mg/kg IV, injection fentanyl 1 ug/kg IV, injection thiopentone 5-6 mg/kg IV, and injection atracurium 0.5 mg/kg IV for intubation with O₂:N₂O @ 40%:60%

and sevoflurane @ 1.5-2% for maintenance titrated to hemodynamic stability. Children below 20 kg were ventilated with Jackson-Rees' modification of Ayer's T-piece and children > 20 kg were ventilated with Bain's circuit.

The principal investigator is the anesthesiologist who loaded all the syringes with the study drugs and prepared them in wrapped aluminum foils and closed envelopes which were provided to another investigator just before administering them to the children. Monitoring and data collection were done by a junior resident who was unaware of the study drugs and allocation.

On arrival at the operating room, standard monitors were applied to every child. Baseline heart rate (HR), respiratory rate, non-invasive blood pressure (NIBP), temperature, electrocardiogram, and SpO₂ were recorded. After securing appropriate IV cannula, all the children were anesthetized with standard GA regimen as mentioned. All the children were ventilated to maintain an ET-CO₂ of 30-35 mmHg. Reversal of neuromuscular blockade was done with glycopyrrolate 20 ug/kg IV and neostigmine 0.7 mg/kg IV on the attainment of signs of reversal. All the study drugs were administered to the children by anesthetist who was unaware of the group allocation, 10 min before the completion of surgery and after discontinuation of sevoflurane. Children were extubated after criteria for extubation was attained.

After extubation children were shifted to post-anesthetic care unit (PACU) and monitored for the following parameters until they were shifted to the ward.

- Hemodynamic parameters: HR, NIBP, and SpO₂.
- Modified objective pain scale (MOPS) scores: Were assessed immediately after extubation and 10 min intervals thereafter in the PACU until they were discharged to the ward. MOPS is intended to evaluate post-operative pain with minimum score 0 and maximum score 10 (represented in Table 1).

Table 1: Modified objective pain score

Observation	Criteria	Points
Crying	No crying	0
	Crying but responds to tender loving care	1
	Crying not responding to tender loving care	2
Movement	None	0
	Restlessness	1
	Thrashing	2
Agitation	Asleep/calm	0
	Mild	1
	Hysterical	2
MOPS score >3	Rescue analgesia required	

MOPS: Modified objective pain scale

- The severity of emergence delirium was evaluated using pediatric anesthesia emergency delirium scale (PAED) with scores ranging from 0 to 20. PAED scale was monitored immediately after emergence and at 10 min intervals thereafter until discharge from PACU (represented in Table 2).
- Adverse reactions at the time of emergence such as nausea, vomiting, laryngospasm, bronchospasm, respiratory depression, desaturation, and bradycardia were noted.
- Emergence time: Time from discontinuation of anesthetic until time to eye opening.
- Duration of sevoflurane anesthesia: Time from the start of sevoflurane for maintenance until the discontinuation of sevoflurane before the end of surgery.
- Time to discharge: Time since arrival at PACU until discharge from PACU to ward.
- Children were monitored in the PACU for all the above parameters until discharge and discharged from the PACU after satisfying the below criteria for discharge.

Criteria for discharge:

1. Fully awake
2. Calm
3. Stable hemodynamics
4. PAED scale < 10
5. MOPS ≤ 3
6. Oxygen saturation > 92% on room air.

Statistical Analysis

Statistical analysis was done with software vassarstats.com. Demographic data were analyzed using Fisher’s exact test. Categorical data were analyzed using *t*-test followed by ANOVA. Data were expressed as mean ± standard deviation, percentage, and absolute numbers. *P* < 0.05 was considered statistically significant.

RESULTS

All the patients who were enrolled in the study completed the study. The three groups were comparable with respect to demographic characters as represented in Table 2, The three groups were comparable with respect to demographic characters as represented in Table 3. High-risk surgeries for emergency agitation such as oropharyngeal and genitourinary procedures were included in this study as mentioned in Table 4.

Intraoperative hemodynamics were comparable in both the groups throughout the surgery, but mean HRs were higher in the control group after extubation and during the immediate recovery period in the PACU when compared with ketofol and dexmedetomidine groups, *P* < 0.001, as

shown in Figure 1. With respect to recovery characteristics such as the duration of surgery, duration of sevoflurane anesthesia, and emergence time, all the three groups were comparable, *P* > 0.05, as represented in Table 5.

Time to discharge was significantly less in dexmedetomidine group compared to ketofol group and significantly less in ketofol group compared to control group, *P* < 0.01, as represented in Table 5. Mean PAED scores were significantly low at arrival, at 10 min, at 20 min, and at 30 min stay at PACU in dexmedetomidine group and ketofol group compared to control group, *P* < 0.01, as represented in Figure 2.

When comparing ketofol and dexmedetomidine groups, the difference in mean PAED scores was clinically significant

Table 2: PAED score

Behavior	Just a little	Quite a bit	Very much	Extremely
Make eye contact with care giver	3	2	1	0
Actions are purposeful	3	2	1	0
Aware of surrounding	3	2	1	0
Restless	1	2	3	4
Inconsolable	1	2	3	4

1-calm, 2-not calm but could be easily consoled, 3-moderately agitated or restless and not easily calm, 4-combative, excited and thrashing around. PAED: Pediatric emergency delirium scale

Table 3: Demographic data

Variable	NS (n=25)	KF (n=25)	D (n=25)	P-value
Age	6.7±2.4	6.7±2.1	6.9±2.2	0.93
M/F	16/9	17/8	12/13	
Wt in kg	21±4.6	20±3.9	21±4.1	0.62
ASA 1/2	17/8	20/5	19/6	

Data expressed as mean, SD, absolute numbers and ratio *P*>0.05, statistically not significant. SD: Standard deviation

Table 4: Type of surgeries

Surgeries	NS (n=25)	KF (n=25)	D (n=25)
Tonsillectomies	5	7	7
Orchiopexy	4	5	3
Herniotomy	6	5	4
Hypospadias	4	3	4
Cleft palate	6	5	7

Data expressed as absolute numbers

Table 5: Recovery characteristics

Time in min	NS (n=25)	KF (n=25)	D (n=25)	P-value
Duration of surgery	62.5±9.6	60.6±7.2	61.3±8.1	0.96
Duration of anesthesia	72.3±9.1	71±10.1	70.8±10.5	0.99
Emergence time	4.3±0.9	4.5±0.7	4.4±0.4	0.56
Time to discharge	45±2.5	32.6±4.3	20±1.5	0.001

Data expressed as mean±SD. A *P*<0.05 was considered statistically significant. SD: Standard deviation

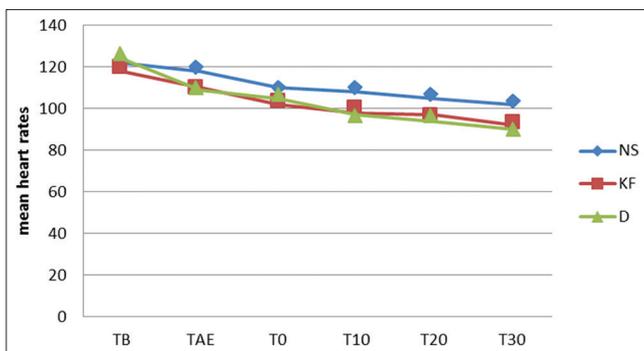


Figure 1: Mean heart rate changes. Data expressed as mean, TB: Time before administering study drug. TAE: Time after extubation, T0: Time at post-anesthetic care unit (PACU) arrival, T10: Time at 10 min PACU, T20: Time at 20 min PACU, T30: Time at 30 min PACU

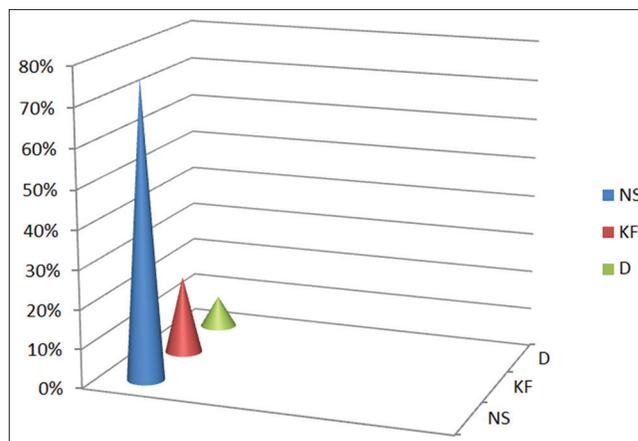


Figure 3: Incidence of emergence agitation. Data expressed as percentage, $P < 0.001$

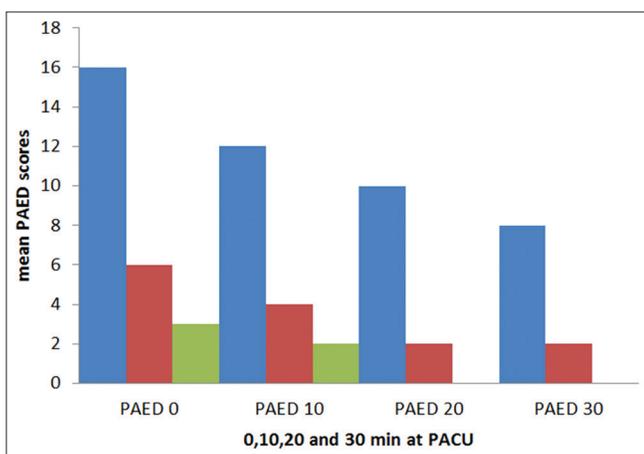


Figure 2: Mean pediatric emergency delirium scale scores during post-anesthetic care unit stay. Data expressed as mean, $P < 0.001$

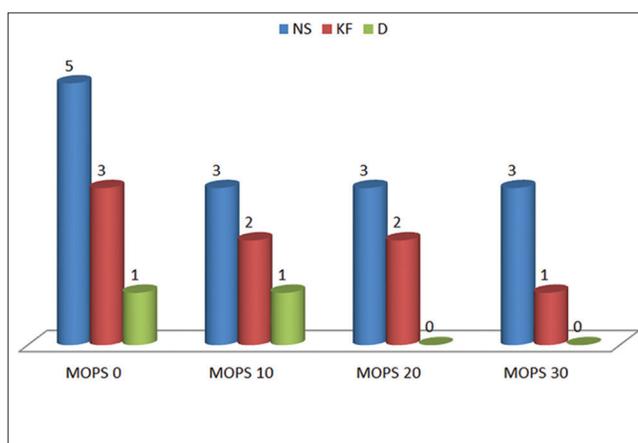


Figure 4: Modified observer pain scale scores. Data expressed as mean modified objective pain scale score at 0, 10, 20, and 30 min at post-anesthetic care unit

but statistically not significant at all these time intervals (mean scores were less in dexmedetomidine group than ketofol group) as represented in Figure 2. The incidence of emergence agitation according to MOPS score >3 and PAED score >10 immediately after emergence was significantly high in the control group, compared to ketofol group and dexmedetomidine group, $P < 0.01$, represented in Figure 3.

The incidence of emergence agitation was less in dexmedetomidine group (8%) compared to ketamine group (20%) but not statistically significant, $P > 0.05$, represented in Figure 3. MOPS scores were significantly high in the control group compared to ketofol and dexmedetomidine group, $P < 0.01$, represented in Figure 4. MOPS scores were clinically comparable between ketofol and dexmedetomidine groups, represented in Figure 4. After 10 min at PACU, MOPS scores were completely zero in the dexmedetomidine group.

12% ($n = 3$) of patients in the control group had vomiting as a side effect, and 8% ($n = 2$) in ketofol group had

transient apnea immediately after extubation which responded to touch. No other side effects were observed in all the three groups.

DISCUSSION

Emergence agitation is defined as number of children with post-operative behavioral disturbances during emergence from sevoflurane anesthesia as measured by agitation scores mentioned in the study. Predisposing factors for emergence agitation include rapid emergence, intrinsic characteristic of the anesthetic, pre-operative pain and anxiety, preschool children, baseline temperament of the child, and the type of surgery. Otolaryngeal, ophthalmic, and genitourinary surgeries carry a high risk of emergence agitation. This study compares pharmacologic interventions aimed at treating pain and anxiety during emergence in pediatric patients posted for various surgeries under sevoflurane-based anesthesia.

This study demonstrates that dexmedetomidine and ketofol reduced the incidence and severity of emergence delirium effectively when compared to normal saline, and the effects of dexmedetomidine being much superior to ketofol.

Dexmedetomidine and ketofol (combination of ketamine and propofol) were preferred in this study because both of them produce sedation and pain relief and help to alleviate emergence agitation in children. Dexmedetomidine, a selective alpha 2 agonist has sedative, analgesic, and anxiolytic effects after IV administration.⁷

Isik *et al.* have shown that dexmedetomidine reduced the incidence of emergence agitation ranging between 4.8% and 17% with no hemodynamic effects after IV administration in doses between 0.3 and 1 ug/kg after induction of anesthesia.⁸ It is proved that α_2 agonists decrease emergence agitation by their analgesia effect as well as by decreasing the anesthetic requirements.

Ketamine, a N-methyl-D-aspartate receptor antagonist, when given in low doses produces effective analgesia and also opioid-sparing effects.⁹ Propofol, an ultrashort acting induction agent, produces sedation in low doses, modifies emergence, and decreases emergence agitation depending on the time of administration.¹⁰ The combination of ketamine and propofol (ketofol) utilizes these two properties to decrease the incidence and severity of emergence agitation which is the rationale for administering this drug in this study. Ketofol also ensures hemodynamic stability along with post-operative analgesia, sedation, and good recovery profile while minimizing the side effects of both agents.¹¹

Ali and Elshorbagy conducted a clinical trial on dexmedetomidine versus ketofol on the incidence of emergence agitation associated with sevoflurane anesthesia and concluded that ketofol (1 mg/kg, 0.25 mg/kg) was as effective as dexmedetomidine 0.3 ug/kg for prevention of emergence agitation but with better analgesic effect and with out delaying emergence.¹²

The results of this study well correlated with the Ali and Elshorbagy study, especially at the end of 30 min of PACU stay. At 10 and 20 min of PACU stay, dexmedetomidine was superior to ketofol as measured by MOPS and PAED scores, but at 30 min of PACU stay, dexmedetomidine is clinically superior to ketofol but statistically not significant with respect to PAED and MOPS scores ($P > 0.05$).

Dahmani *et al.*, in their meta-analysis on emergence agitation, have shown that pain prevention, propofol, fentanyl, ketamine, and α_2 agonists have preventive effects

on emergence delirium while midazolam and serotonin inhibitors did not have a prophylactic effect.¹³

Patel *et al.* compared dexmedetomidine infusion versus IV fentanyl and concluded that dexmedetomidine infusion significantly reduced the post-operative opioid requirements and incidence and severity of emergence agitation in children undergoing tonsillectomies and adenoidectomies.¹⁴

Guler *et al.* showed that in dexmedetomidine group, the time to extubation and the time to discharge from PACU were prolonged compared to ketofol and control groups contrary to the current study where the time to extubation was comparable between all three groups, but time to discharge is significantly less in dexmedetomidine group than ketofol and control groups, where attenuation of pain and anxiety could be the factors responsible for early attainment of discharge criteria in dexmedetomidine group.¹⁵

Sikich and Lerman developed the PAED to assess the incidence and severity of emergence agitation by incorporating cognitive and agitation elements and proved its reliability and validity. Most of the studies used PAED score to assess emergence agitation¹⁶. In this study, we have used PAED score compounded with MOPS as assessment tools to emergence agitation.

Aouad *et al.* demonstrated that the threshold score for PAED score was 10 which was the best discriminator between presence and absence of emergence agitation (incidence).¹⁷

PAED score of > 16 and MOPS of > 3 at any point of time during the first 30 min of PACU stay represent severe agitation in this study.

The incidence of emergence agitation is significantly high in the control group compared to ketofol or dexmedetomidine group during children's stay in the PACU until discharge in the current study. At the end of 30 min of PACU stay, the incidence is gradually decreased probably due to the weaning effect of sevoflurane. Fentanyl 1 ug/kg was administered as rescue agent to produce analgesia and sedation to all children whose has MOPS scale > 3 and PAED score > 10 after 30 min of PACU stay in this study. Children who had vomiting episode in the PACU were administered on dansetron 0.1 mg/kg IV.

Significant changes in the hemodynamics occurred after extubation in the control group when compared to ketofol and dexmedetomidine group which can be due to the sympathetic responses triggered by

immediate post-operative pain in the placebo group. The hemodynamics after extubation and during PACU stay were comparable between ketofol and dexmedetomidine group. Probably, the low doses of study drugs could be responsible for the hemodynamic stability in ketofol and dexmedetomidine groups.

Lack of validated uniform outcome scales as a tool to measure emergence agitation can be a limitation in this study. Effect of pain on children's behavior was a potential confounder in determining the outcome. There is a lot of scope for the future studies and interventions which should include control group and ensure that control group should be given adequate analgesia for which pain may be a confounding factor in the incidence of emergence agitation.

CONCLUSION

Dexmedetomidine (0.3 ug/kg) and ketofol (0.25 mg/kg and 1 mg/kg) caused a significant reduction in the incidence and severity of emergence agitation when compared to control group. Ketofol was as effective as dexmedetomidine in the prevention of emergence agitation when administered before the end of surgery, but children administered dexmedetomidine was calm and satisfied discharge criteria earlier than ketofol at this low dose.

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