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Research Article

Use of ketofol to control emergence agitation in children undergoing adenotonsillectomy

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KEYWORDS
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Abstract Objective: To assess the efficacy and safety of ketofol administration in controlling emergence agitation (EA) after sevoflurane-based anesthesia in children undergoing adenoidectomy or adenotonsillectomy.
Subjects and methods: This double-blinded randomized study involved 90 children (3–6 years) scheduled for elective adenotonsillectomy or adenoidectomy. They were randomly assigned to receive 10 ml of normal saline (control group, C) or, 1 mg/kg propofol in 10 ml saline (group P) or ketofol as 1 mg/kg propofol and 0.25 mg/kg ketamine in 10 ml saline (group K) 10 min before the end of surgery. In PACU, sedation, behavior, pain and severity of EA were assessed using modified Aldrete score, Aono's scale, Objective Pain Score (OPS) and Pediatric Anesthesia Emergence Delirium (PAED) scale, respectively.
Results: In ketofol group, OPS was significantly lower compared to propofol and control groups. Recovery criteria were in favor of ketofol and propofol groups including longer time to eye opening ($p < 0.001$) and time to Aldrete score P 9 ($p = 0.001$). Time to discharge from PACU was comparable in the three groups ($p = 0.079$). EA was significantly more frequent in the control group ($p < 0.001$), but comparable in ketofol and propofol groups. PAED score was significantly higher in control group compared to ketofol and propofol groups. Ketofol and propofol preserved hemodynamic stability.
Conclusion: Ketofol provides a promising new option for controlling emergence agitation with adequate postoperative sedative and analgesic effect, good recovery criteria and hemodynamic stability compared to propofol and control groups in children undergoing adenoidectomy or adenotonsillectomy.

1. Introduction

Emergence agitation (EA) designates an irritable, uncooperative, and inconsolable child upon emergence. It can be linked with a number of causes including pain, anxiety and psychological compromise in addition to anesthetics side effect [1]. EA may increase the risk of falling, bleeding and self-extubation. Continuous monitoring in the recovery room and drug

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administration or physical restriction of the patient may be needed to control EA [2].

Sevoflurane has been broadly used in pediatric anesthesia. However, EA is a common side effect of sevoflurane anesthesia with varying incidence from 10% to 66% [3,4]. Rapid recovery is suggested as one of the factors causing EA after sevoflurane anesthesia, which was not proved with gradual decrease in sevoflurane [5] and in comparison with other drugs with rapid awakening [6].

Effective prevention of EA has been previously investigated with fentanyl [7,8], clonidine [9], oxycodone [10], dexmedetomidine [11,12], midazolam [13], ketamine [14,15], propofol [16–18] and remifentanil [19].

Propofol is a non-opioid, non-barbiturate, sedative-hypnotic agent with rapid onset and short duration of action [20]. Ketamine is a phencyclidine derivative classified as a dissociative sedative that provides analgesia and amnesia [21–23]. Combining ketamine with propofol reduces the sedative dose of propofol. The complementary effects of this combination are supposed to produce lower toxicity compared to each drug alone through decreasing required doses [22]. Ketofol; mixed ketamine and propofol has been shown to be effective in emergency room for procedural sedation [24–31] and for induction for rapid sequence intubation.

Both drugs; propofol and ketamine were used separately successfully to control emergence agitation in adults and children. We suggest effective prevention of EA with a combination of ketamine and propofol; ''ketofol'' in pediatric patients undergoing simple surgical procedural in addition to the advantage of better hemodynamic stability.

The aim of this double-blinded randomized study is to assess the efficacy and safety of ketofol administration in decreasing or preventing EA after sevoflurane-based anesthesia in children undergoing adenotonsillectomy in comparison with administration of propofol alone with assessment their hemodynamic stability.

2. Subjects and methods

This study was conducted in Abu EI-Rish Hospital, Cairo University from 2010 to 2012. After ethical committee approval and obtaining written parental informed consent, 90 children aged 3–6 years, ASA physical status I or status II scheduled for elective adenotonsillectomy or adenoidectomy were studied. We excluded children with heart disease, chest infection and neuropsychiatric illnesses.

Using closed envelope method, children were randomly assigned to receive 10 ml of normal saline; control group (C), or 1 mg/kg propofol in 10 ml saline; group (P), or ketofol prepared as 1:0.25 mg/kg of propofol to ketamine respectively in 10 ml saline; group (K). An assistant anesthesiologist not involved in the data collection prepared the syringe for each patient. Children received atropine 0.02 mg/kg intramuscularly 30 min before induction of anesthesia as premedication. Upon arrival to the operating room, standard monitors including electrocardiogram, non-invasive blood pressure and pulse oximeter were attached (Infinity SC 8000, Drager medical system, Avenue, Danvers, MA, USA). The baseline readings were recorded as (T0).

Anesthesia was induced in all patients with 5–8% sevoflurane (Sevorane, Abbott Laboratories SA, Abbott Park, IL, USA) in oxygen through facemask. After obtaining a sufficient depth of anesthesia, a peripheral intravenous line (22G) was inserted and fentanyl 2 lg/kg and atracurium 0.5 mg/kg were administered to facilitate endotracheal intubation. Anesthesia was maintained using sevoflurane inhalational anesthetic. Mechanical ventilation was performed to sustain end tidal ET CO_2 at 30–35 mmHg. Ondansetron 0.1 mg/kg and dexamethasone 0.2 mg/kg were given as standard antiemetic for all patients.

Ten minutes before the completion of the procedure, the study drugs were administered to the patients by an anesthetist not involved in the study. The syringe of the study drug was wrapped in foil to ensure blindness to the administered agent. Children in group C were given 10 ml saline; those in group P were given 1 mg/kg propofol in 10 ml saline while those in group K received 1 mg/kg propofol mixed with ketamine 0.25 mg/kg in 10 ml saline. Intraoperative HR and MAP were recorded after induction of anesthesia (T1) and 5 min after drug administration (T2).

Sevoflurane anesthesia was discontinued and manual ventilation was performed. Residual muscle relaxation was reversed using prostigmine 0.05 mg/kg and atropine 0.02 mg/kg. Patients were extubated when they opened their eyes with full recovery of spontaneous breathing (tidal volume 8 ml/kg, respiratory rate more than 12/min, normal breathing pattern and good oxygenation SpO_2 more than 98%). The time to eye opening from stopping of anesthetics was measured.

Parents were allowed to stay with their children in the PACU. During PACU stay MAP, HR and SpO_2 were continuously monitored. MAP and HR were recorded upon arrival to the PACU, at 10, 20 min. postoperatively and on PACU discharge (T3–T6). If oxygen saturation fell below 95%, oxygen facemask was given to the child.

Modified Aldrete score (0–10 point scale) [19] was used to monitor sedation on PACU admission and at 5 min interval. Time to achieve full Aldrete (P9) was recorded. Children's behavior was evaluated on PACU admission using Aono's scale (Table 1) [32]. Agitation score of 3 or 4 was considered as an agitation episode. The severity of EA was evaluated using Pediatric Anesthesia Emergence Delirium (PAED) scale (Table 2) [33] which provide a score from (0–20) upon arrival to PACU, at 10 and 20 min postoperatively then on PACU discharge (T3–T6). Postoperative pain was assessed at the same time intervals using Objective Pain Score (OPS) (Table 3) [34]. Each criterion scored from (0–2) to give a total score of (0–10). If OPS is 4 or more, 1–2 mg/kg diclofenac suppository was administered. Midazolam 0.1 mg/kg intravenously was given to treat agitation without pain.

Children were discharged from PACU after satisfying discharge criteria of being calm, fully awake, minimum pain, stable vital signs and oxygen saturation >95% on room air. Discharge time that was defined as the time from PACU admission until the child fulfilled the discharge criteria was recorded. Recovery was assessed in terms of time to eye opening,

Table 1 Aono's four-point scale [32].

Calm	1
Not calm, but could be easily calmed	2
Moderately agitated or restless	3
Combative, excited, disoriented	4

Table 2 Pediatric Anesthesia Emergence Delirium (PAED) scale [33].

	Not at all	Just a little	Quite a bit	Very much	Extremely
1. The child makes eye 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 3 Objective Pain Scale (OPS) [34].

Parameter	Points
Systolic blood pressure	
Increase < 20% of preoperative blood pressure	0
Increase 20–30% of preoperative blood pressure	1
Increase > 30% of preoperative blood pressure	2
Crying	
Not crying	0
Responds to age appropriate nurturing (tender loving care)	1
Does not respond to nurturing	2
Movements	
No movements relaxed	0
Restless moving about in bed constantly	1
Thrashing (moving wildly)	2
Rigid (stiff)	2
Agitation	
Asleep or calm	0
Can be comforted to lessen the agitation (mild)	1
Cannot be comforted (hysterical)	2
Complains of pain	
Asleep	0
States no pain	0
Cannot localize	1
Localizes pain	2

time to achieve full Aldrete, discharge time and frequency of emergence agitation.

3. Statistical analysis

Data were analyzed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using independent sample t-test or Mann–Whitney test. Two-way ANOVA was used to compare repeated measures in the three groups. In case of group interaction, comparison between 3 groups was done using ANOVA test, then post-Hoc ''Scheffe's test'' was used for pair-wise comparison. Comparison of consecutive measures was done using ANOVA for repeated measures. A p-value < 0.05 was considered significant.

4. Results

The three studied groups were comparable in the demographic and clinical characteristics (Table 4). Before induction of anesthesia (T0), there was no significant difference between the three groups in MAP and HR. After induction of anesthesia decrease in MAP and HR was observed in the three groups. In control groups mild fluctuations were observed up to T6. After study drug administration (T2), significant decrease in MAP and HR was observed in groups P and K compared to baseline values and to group C values. However, all the changes were within the clinically accepted ranges (±20% of baseline). Compared to control group ketofol and propofol groups showed significantly lower values of MAP and HR on arrival to the PACU and after 10 min (T3 and T4). Comparable values were observed afterward (Figs. 1 and 2).

In ketofol group, OPS was significantly lower compared to propofol and control groups on admission to the PACU and 10 and 20 min later. On discharge the OPS became comparable in the three groups (Table 5). Recovery criteria were in favor of ketofol and propofol groups (table 6) including longer time to eye opening (p < 0.001) and time to Aldrete score P 9 (p = 0.001). Time to discharge from PACU was comparable in the three groups (p = 0.079). EA, i.e. Aono's score 2 or 3 significantly more frequent in the control group (p < 0.001) compared to ketofol and propofol groups, but the latter two groups were comparable. Similarly, PAED score was significantly higher in control group compared to ketofol and propofol groups on admission to PACU and 10 min. later (Table 7). Also, PAED score was comparable between ketofol and propofol groups.

5. Discussion

This study showed that combined ketamine and propofol (ketofol) reduced the frequency of emergence and delirium in sevoflurane-anesthetized children undergoing tonsillectomy as effective as propofol alone. It ensured adequate postoperative sedation and analgesia with good recovery criteria and hemodynamic stability. In addition, ketofol showed superior analgesic effect during the immediate postoperative period as shown in OPS.

In the literature, the prevalence of emergence agitation in children ranges from 10% to 66% with different types of inhalation anesthetics [3,4,35]. In fact, this is not a new clinical phenomenon; nevertheless, the etiology is not yet definitively elucidated. Pain is one of the possible causes in addition to preoperative anxiety, type of anesthetics and type of surgical procedures [36].

Conflicting researches were stated in effectiveness of propofol in EA. Some previous studies reported effectiveness of propofol as an adjunct to sevoflurane in reduction in EA [37,38]. However other studies found no significant effect of propofol 1 mg/kg in reducing incidence and severity of EA in children, especially in this surgical category as tonsillectomy, under sevoflurane anesthesia [39].

Table 4 Demographic data in the three studied groups.

	Ketofol group n = 30	Propofol group n = 30	Control group n = 30	p-Value
Age (years)	4.3 ± 1.5	4.7 ± 1.5	4.1 ± 1.3	0.263
Weight (kg)	25.4 ± 3.6	26.3 ± 3.2	24.9 ± 4.7	0.372
Sex (male/female)	18/12	16/14	13/17	0.429
ASA (I/II)	25/5	26/4	27/3	0.749

Date as mean ± SD or number and ratio.

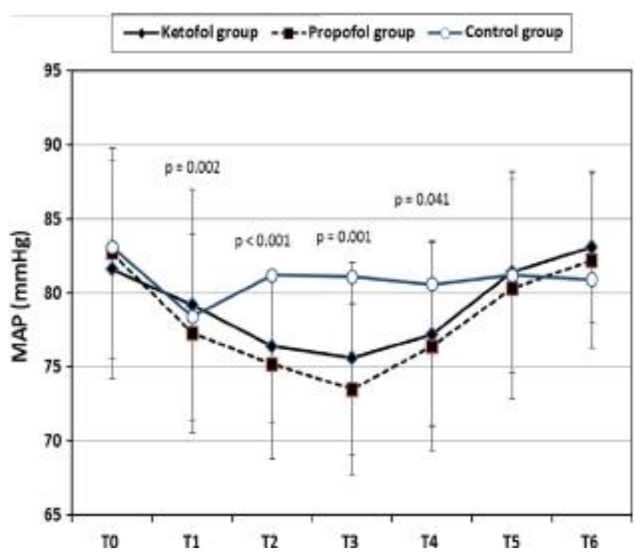

Figure 1 Changes in mean arterial pressure from baseline to discharge from postanesthetic care unit in the three studied groups. T0 (baseline), T1 (after induction of anesthesia), T2 (5 min after drug administration), on arrival to the PACU, at 10, 20 min. postoperatively and on PACU discharge (T3–T6). A p-value < 0.05 was considered significant.

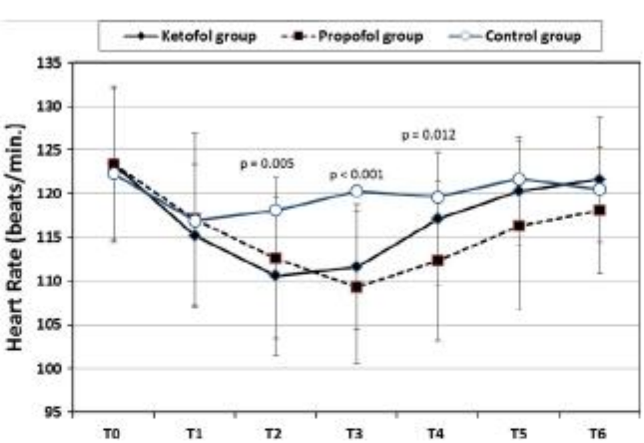

Figure 2 Changes of heart rate from baseline to discharge from postanesthetic care unit in the three studied groups. T0 (baseline), T1 (after induction of anesthesia), T2 (5 min after drug administration), on arrival to the PACU, at 10, 20 min. postoperatively and on PACU discharge (T3–T6). A p-value < 0.05 was considered significant.

Although several reports showed a significant lower pain scores on addition of ketamine [40], however others showed that ketamine, when added to fentanyl versus propofol–fentanyl combination had actually significantly higher PAEDS scale score after cataract surgery [41]. On the other hand, reports demonstrated that administration of ketamine after the induction of anesthesia or before the end of surgery effectively reduced the incidence of EA without significant hemodynamic adverse effects [15,42–44].

Ketofol was previously reported to be effective for pediatric procedural sedation. It was tried successfully in children requiring closed fractures reduction [45–48], incision and drainage of abdominal wall abscess [49], suturing, foreign body removal and chest tube insertion [50]. In the current study we believed that the analgesic effects of ketamine added to the sedative properties of propofol make ketofol a tempting option to control emergence agitation and delirium in this type of procedures. To our knowledge, this study is the first blinded randomized controlled trial to compare ketamine–propofol to propofol alone for control of emergence agitation following adenotonsillectomy.

Ketofol as well as propofol in the current study was significantly effective in reducing the frequency of EA compared to control group. The lowest frequency was in favor of ketofol despite the non-significant difference with propofol.

Pain causes the release of stress hormones which may produce an increase in metabolic rate, heart rate and blood pressure [51]. Unrelieved pain prolongs the stress response and may discourage performing recovery activities as deep breathing leading to hypoxia, hypercarbia and agitation [52]. However, previous studies found that pain management did not alter the risk for postoperative agitation [53–55].

The results of this study confirmed the analgesic effect of ketofol evidenced by lower objective pain score in the PACU in ketofol group compared to propofol alone. We believe that analgesic properties of ketamine contribute to the good recovery profile in the study sample, despite the non-significant difference in frequency of emergence agitation. Previous studies designate the role of pain in causing EA in children. In a group of children undergoing surgery on the thigh, fascia iliaca compartment block not only improved the postoperative pain scores, but also reduced the severity of emergence agitation [56]. Also in another study, the analgesic properties of dexmedetomidine may explain its efficacy in reduction in EA following tonsillectomy in children [12].

Ketamine when added to propofol in the present study combined the analgesic effect of ketamine and sedative effect of propofol with a reduction in the dose of medication needed for both. Thus, this combination enhanced the advantages of sedation and analgesia without compromising the hemodynamic stability or increasing side effects of either drug alone.

We conclude that this preliminary study using ketofol for controlling emergence agitation and delirium provides a promising new option compared to propofol in children undergoing

Table 5 Median value of Objective Pain Score (OPS) in the three studied groups in the postanesthetic care unit (PACU).

	Ketofol group n = 30	Propofol group n = 30	Control group n = 30	p-Value
On PACU admission	4 (0–5)^{a}	4 (2–6)^{b}	5 (2–6)^{b}	0.032
After 10 min	2 (0–5)^{a}	3 (0–6)^{b}	3 (1–6)^{b}	0.002
After 20 min	2 (0–4)^{a}	3 (0–4)^{b}	3 (0–5)^{b}	0.001
On PACU discharge	2 (0–3)	2 (0–3)	2 (0–3)	0.321

Date as median (range).
Groups with different superscript letters are significantly different.
A p-value < 0.05 was considered significant.

Table 6 Recovery criteria and frequency of emergence agitation (EA) in the three studied groups.

	Ketofol group n = 30	Propofol group n = 30	Control group n = 30	p-value
Time to eye opening (min)	10.5 ± 2.2^{a}	9.8 ± 2.8^{a}	8.2 ± 1.6^{b}	0.001
Time to full Aldrete score (min)	13.8 ± 1.8^{a}	14.1 ± 1.6^{a}	11.9 ± 2.3^{b}	<0.001
Time to discharge from PACU (min)	36.8 ± 6.9	38.5 ± 7.7	40.4 ± 8.6	0.205
Frequency of agitation, no. (%)	5 (16.7%)^{a}	7 (23.3%)^{a}	19 (63.3%)^{b}	<0.001

Date as mean ±SD Date or number and percent.
Groups with different superscript letters are significantly different.
A p-value < 0.05 was considered significant.

Table 7 Median value of Pediatric Anesthesia Emergence Delirium (PAED) score in the three studied groups in the postanesthetic care unit (PACU).

	Ketofol group n = 30	Propofol group n = 30	Control group n = 30	p-value
On PACU admission	6 (0–13)^{a}	8 (0–13)^{a}	13 (6–17)^{b}	<0.001
After 10 min	3 (0–6)^{a}	4 (0–6)^{a}	7 (1–9)^{b}	0.012
After 20 min	2 (0–3)	2 (0–4)	3 (0–5)	0.232
On PACU discharge	0 (0–3)	0 (0–3)	1 (0–3)	0.487

Date as median (range).
Groups with different superscript letters are significantly different.
A p-value < 0.05 was considered significant.

adenoidectomy or adenotonsillectomy. It has an adequate postoperative sedative and analgesic effect with good recovery criteria and hemodynamic stability. Further larger studies in different types of surgeries with short term recovery in children are needed to confirm the current results. More research is still required to elucidate the exact mechanism of emergence agitation for switch to the appropriate targeted treatment of this complication responsible for postoperative morbidities in pediatric surgery.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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