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Research Article

Effects of Ketofol Intravenous Anaesthesia versus Isoflurane on Emergence Agitation in Children Undergoing Cataract Extraction

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ABSTRACT

Objectives: Emergence agitation is a common post-operative complication in children following the use of inhalational anesthetic agents. The study was designed to evaluate the effects of Ketofol TIVA and isoflurane on the incidence and severity of Emergence Agitation (EA) in children who had cataract surgery.

Methods: Ninety-four patients between the ages of two and six years with American Society of Anaesthesiologist (ASA) physical status 1 or 11 undergoing elective cataract surgery under general anesthesia were randomised into two groups of 47 patients each. Induction of anaesthesia was with 2-3 mg/kg of propofol in both groups. One group of patients (group A) was maintained with ketofol TIVA in the ratio of 1:10 (1 mg/kg/hr of ketamine and 10 mg/kg of propofol) while the second group was maintained on 1-1.2 MAC of isoflurane. The incidence and severity of Emergence Agitation (EA) were assessed in the first one hour of the post-operative period using the Pediatric Emergence Delirium (PAED) scale. The emergence, extubation and recovery time were also assessed every 5 minutes and compared using Fisher's exact test. The complications related to the two techniques of maintenance of anaesthesia in the first hour of the PACU stay were reported.

Results: The two groups had similar age and weight characteristics. In group A, 2 patients (4.3%) had EA while 10 patients (21.3%) had same in group B ($p<0.005$) from baseline time (T0) to 15 minutes postoperatively (T15). The median PAED score was statistically significant at T0 ($p= 0.004$). There was no statistical difference between the emergence, extubation and recovery times. Retching, vomiting and laryngospasm in both groups were not statistically significant.

Conclusion: Ketofol TIVA in the ratio of 1:10 reduced the incidence and severity of EA following cataract extraction in the first one hour of the post-operative period when compared with isoflurane as maintenance anaesthetics.

Keywords: Ketofol (TIVA); Isoflurane; Emergence agitation; Children; Cataract surgery

INTRODUCTION

Emergence Agitation (EA) or Emergence Delirium (ED) is a common post-operative anaesthetic complication in children recovering from general anaesthesia [1]. Despite the awareness of this post anaesthetic problem for the past 50 years; it is still a subject of interest in pediatric anaesthesia. The incidence in children is as high as 80% [2]. EA is characterized by mental confusion, disorientation, irritability, inconsolability, excessive crying, restlessness, pulling out of wound dressing, intravenous access and other attached monitoring equipment [3]. This is associated with increased anxiety and concern in the parents/guardians as regard the clinical condition of their children. The attending health care giver can also be a victim of assault ranging from scratch marks on the body to human bite, while the child can be self-injured.

EA is self-limiting, sometimes lasting about 3-45 minutes, and resolving spontaneously in most cases [3]. It has also resulted in prolonged Post Anesthesia Care Unit (PACU) stay and reports of adverse events such as increased bleeding and pain from surgical site have also been documented [3]. The exact cause is unknown but the major factor that has been associated with the

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occurrence of EA following general anesthesia in children is the use of volatile-based anaesthetic agents [1,3,4].

There is paucity of data about the incidence of EA with the use of isoflurane in West African sub region. Other factors that have been implicated as causes of EA include post-operative pain even though EA may be seen in children undergoing non-painful procedures under sevoflurane anaesthesia [5], pre-school children, preoperative anxiety, otolaryngology and ophthalmic procedures [3].

Ketamine is an intravenous anaesthetic agent with good hypnotic, sedative and analgesic property. Its analgesic property can be used as an adjunct to propofol TIVA. Propofol in combination with ketamine ("ketofol") has good sedating, analgesic and stable haemodynamic effects [6]. Ketofol has been mainly used for procedural sedation in children and adult [7,8]. There is a dearth of literature on the use of ketofol TIVA for maintenance of anaesthesia for the purpose of preventing EA, although both drugs (ketamine and propofol) have been used separately as boluses given at the end of sevoflurane anaesthesia for the prevention of EA [9].

Considering the good properties of ketofol, the aim of this randomised controlled study is to compare the effects of maintenance of anaesthesia with ketofol TIVA versus isoflurane anaesthesia on the incidence and severity of EA in children undergoing cataract extraction in our environment.

METHODS

Intraoperative care

The study was a prospective single blind (research assistants) randomized trial of two groups of children undergoing cataract extraction. Approval by the appropriate Research Ethical Committee and written informed patient consent was obtained from parent/guardian. Pediatric patients aged 2-6 years scheduled to have cataract surgery and whose parents/guardian had given informed consent for the procedure were assessed for eligibility and declared fit for the procedure

The attending anaesthetist and the patient were not blinded to the technique of anaesthesia. All the patients were induced with 2 to 3 mg/kg of propofol Baseline vital signs including non-invasive blood pressure, heart rate, respiratory rate, temperature; 5-lead ECG and peripheral oxygen saturation were obtained. In addition to standard monitoring the disposable Bispectral index (BIS) sensor (Aspect medical system, VISTA MA USA) was applied to the patient's forehead before induction of anaesthesia and this was connected to a BIS monitor model A-2000 TM to monitor the depth of anaesthesia or hypnotic state of the patient. All the patients were given anti-emetic prophylaxis using 0.1 mg/kg of dexamethasone and preoxygenated through a face mask *via* Ayre' T piece with Jackson Ree's modification or Bain's circuit if the child weighed more than 25 kg.

Anaesthesia was maintained in group A with ketofol using McFarlan infusion dose regimen (15 mg/kg/h for 15 min, 13 mg/kg/h for 15 min, 11 mg/kg/h for 30 min) and infusion rates were decreased by 90% of the ratio 1:10. The study medication was prepared by the same anaesthetist for each of the patients. Group B patients were maintained with 1-1.5 MAC of isoflurane.

Muscle relaxation was achieved with pancuronium at 0.1 mg/kg. The airway was secured with appropriate size endotracheal tube after the confirmation of correct placement of the tube. Patients in Group A were maintained on ketofol (1 mg/kg/hr of ketamine) and propofol 10 mg/kg/hr (ratio 1:10) infusion through a B Braun infusion (GSA DIA MEDICAL USA) pump using McFarlan infusion dose regimen. Those in Group B were maintained on 1-1.5 minimum alveolar concentration (MAC) of isoflurane in 100% oxygen. All the patients were mechanically ventilated *via* a closed-circuit breathing system.

Haemodynamic parameters such as blood pressure, heart rate and oxygen saturation were monitored continuously and recorded at an interval of 5 minutes. Depth of anaesthesia was also monitored and the target BIS value was 40-60. BIS value above 60 was regarded as awareness under anaesthesia and this was managed with administration of bolus doses of ketofol infusion in group A, and increase in the fractional inspired concentration of isoflurane in group B. At the end of the procedure, the ketofol infusion or isoflurane was discontinued and residual neuromuscular blockade was reversed with 0.05 mg/kg of neostigmine in addition to an anticholinergic agent (0.01 mg/kg of atropine). Suctioning under direct vision was done and tracheal extubation was done. The intravenous access of group A (Ketofol) was flushed with 10 mls of sterile water before going into the recovery room to avoid bias by the observer.

Post-operative care

Patient were transferred with oxygen to the recovery room when they have fully recovered from anaesthesia and were allowed to have contact with one of the parents or care giver during the period of stay in the PACU. All the patients were assessed for post-operative emergence agitation every 5 minutes for the first one hour after surgery by the research assistant using the Paediatric Anaesthesia Emergence Delirium (PAED) scale. The primary outcome variable was a PAED score of greater than 10. Secondary outcomes were intraoperative hemodynamic changes (heart rate, blood pressure, and mean arterial blood pressure), postoperative recovery profile (time of recovery, emergence and extubation time and occurrence of vomiting). Intravenous paracetamol 15 mg/kg 8 hourly was given for post-operative analgesia. The time of readiness for discharge was assessed using modified Aldrete scoring system. Other parameters that were assessed include emergence

Data collection

Data was collected using a data collection proforma designed for the purpose of the study. All the participants' bio-data, intraoperative haemodynamic were recorded. The primary outcome variable was a PAED score of greater than 10. Secondary outcomes were intraoperative haemodynamic changes (heart rate, blood pressure, and mean arterial blood

pressure), postoperative recovery profile (time of recovery, emergence and extubation time and occurrence of vomiting).

Data analysis

Block randomisation was performed using computer generated table of random numbers with online software. The calculated sample size was randomly divided into an equal group of two. Consecutive patients were allocated to the group they belong in order of enlistment.

Qualitative variables were represented using tables and charts in frequency and percentages while quantitative data was presented in descriptive format (mean and standard deviation). Test of associations for categorical variables was done using Chi square test while Fisher s exact test was used when the expected value of a single is less than five. To test the difference between means and median between the two groups, an independent sample t - test and a non-parametric independent t-test (Mann-Whitney U) was performed. The level of significance was declared when (P-value was found to be less than 0.05.)

RESULTS

One hundred ASA I and II children aged between 2-6 years were eligible and approached for the study, out of which six of the patients were excluded from the study because the patients/ guardians refused to give consent. Therefore, data from 94 patients (47 in each group) were analyzed.

The socio-demographic characteristics of the patients showed a similar mean age of 5.2 ± 0.9 years and 5.2 ± 1.0 years in group A and B group respectively. There were 33 males and 14 female in the group A compared to 30 males and 17 females in Group B, P=0.510. The mean weight was 18.9 ± 3.9 kg and 19.2 ± 4.9 kg in group A and group B respectively and this was not statistically significant All the patients in group A were ASA 1, while one patient in group B was ASA class II.

Indication for surgery in the two groups were similar with trauma to the eye constituting over (50%) in both groups, less than a tenth had congenital cataract (6%) while developmental cataract was the indication in about 30% of the study population.

The proportion of children with previous exposure to surgery and anesthesia, though higher in group A (14.9%) compared to group B, it was not statistically significant (p=0.336). Mean duration of surgery was 41.2 ± 6.9 minutes in group A and 43.6 ± 11.7 minutes in group B (p=0.241).

Also, the mean duration of anesthesia was 70.6 ± 12.6 minutes in group A and 68.4 ± 16.1 minutes in group B (p=0.461) as shown in Table 1.

Table 1: Demographic and clinical data of the patients.

Variable	Group A (Ketofol)	Group B (Isoflurane)	
	N=47	N=47	P-value
	n (%)	n (%)	
Age (years) (mean ± SD)	5.2 ± 0.9	5.2 ± 1.0	#0.833
Gender			^0.510
Male	33 (70.2)	30	
Female	14 (29.8)	17	
Weight (Kg) (mean ± SD)	18.9 ± 3.9	19.2 ± 4.9	#0.522
Indication for Surgery			
Trauma cataract	26 (55.3)	27 (57.4)	^0.977
Congenital cataract	3 (6.4)	3 (6.4)	
Developmental cataract	18 (38.3)	17 (36.2)	
Duration of surgery (mins) (mean ± SD)	41.2 ± 6.9	43.6 ± 11.7	#0.241
Duration of Anaesthesia (mins) (mean ± SD)	70.6 ± 12.6	68.4 ± 16.1	# 0.461

#Independent T-test, ^ Chi-square test, f Fisher's exact test

On arrival in PACU (T0), the overall incidence of emergence agitation was 12.8% (12/94) and distributed as 2 (4.3%) patients in group A and 10 (21.3%) patients in group B, p=0.013 (Table 2). At T5 minutes, the 2 patients in group A observed to have agitation at T0 were still agitated and same was observed in the 10 patients in group B who were still agitated, this was statistically significant (p=0.013). At T10 minutes, one of the 2 patient in group A and 6 patients in group B still had agitation, though this was not statistically significant, P=0.111. At T15 minutes, one patient in each group still had agitation, p=1.000. From T20 to T60, emergence agitation had resolved in the 12 patients observed initially at T0 (Table 2).

Table 2: Comparison of emergence agitation (PAED score>10).

Time (mins)	Group A (Ketofol)	Group B (Isoflurane)	Total	P-value
T0	2 (4.3)	10 (21.3)	12	0.013*
T5	2 (4.3)	10 (21.3)	12	0.013*
T10	1 (2.1)	6 (12.8)	7	0.111f
T15	1 (2.1)	1 (2.1)	2	1.000f
T20-T60	0 (0.0)	0 (0.0)	-	NA

T0=Baseline (Arrival at PACU)

T5=5 minutes in the PACU

T10=10 minutes in the PACU

T15=15 minutes in the PACU

T20-T60 = 20-60 minutes in the PACU

Severe emergence agitation measured with PAED score of >15 was observed only in patients in group B. At T0, there were three patients with severe agitation and this reduced to one patient at T5 while no patient had continued agitation after T5 (Table 3 and Table 4).

Table 3: Severity of emergence agitation (PAED score >15).

Time (mins)	Group A (Ketofol)	Group B (Isoflurane)	Total	p-value
T0	0 (0.0)	3 (6.4)	3	0.242 f
T5	0 (0.0)	1 (2.1)	1	1.000 f
T10-T60	0 (0.0)	0 (0.0)	0	NA

N=Number of patients with PAED score >15, f Fisher's exact test, NA-Statistics not applicable

Table 4: Comparison of PAED scores in the two groups.

Time	Group A (Ketofol)	Group B (Isoflurane)	P-value
(mins)	Median(IQR)	Median(IQR)	
T0	9 (1)	9 (2)	0.004*
T5	9 (2)	9 (3)	0.308
T10	8 (3)	8 (4)	0.966
T15	6 (0)	6 (9)	0.758

T20-T60	0 (0)	0 (0)	NA

*Statistical significance at p<0.05, Mann-Whitney U, NA- Statistics not applicable

The mean emergence time was 5.9 and 5.1 minutes in group A and group B respectively, P=0.058. The mean time to extubation was of 7.6 ± 3.1 minutes in group A and 6.8 ± 4.4 minutes in group B, P=0.301 while the recovery time was 30.3 ± 10.6 minutes and 26.5 ± 13.5 minutes in group A and B respectively, p=0.136 (Table 5).

Table 5: Recovery characteristics.

Variables	Group A (Ketofol)	Group B (Isoflurane)	P-value
	Mean (SD)	Mean (SD)	
Emergence time (mins)	5.9 (3.1)	5.1 (4.2)	0.058
Extubation time (mins)	7.6 (3.1)	6.8(4.4)	0.301
Recovery time (mins)	30.3 (10.6)	26.5 (13.5)	0.061

*Statistical significance at p<0.05, Mann-Whitney U, NA-Statistics not applicable.

DISCUSSION

The main finding in this study was a reduction in the incidence and severity of EA when low dose ketamine- propofol combination was used for maintenance of anaesthesia as compared to isoflurane in children who had cataract surgery. Ketofol has been documented by many authors to be more effective in reducing the incidence and severity of EA in both children and adult when compared to inhalational agent [10,11,12]. EA typically occurs in children following rapid recovery from the effect of inhalation anaesthetic agent hence, the suggested mechanism for the beneficial effect of ketofol is the sedating and analgesic effect of ketamine in combination with the sedating effect of profofol in the immediate post-operative period.

The overall incidence of emergence agitation was 12.8%, this falls within the established range of 2-80% incidence reported generally in children with the use of different anaesthetic agents [13]. Inhalational agents have been the main implicating factor in the pathogenesis of EA. The exact mechanism responsible for EA is not fully understood however, rapid wash out or recovery as evidence by the occurrence of abnormal EEG changes has been implicated with the use of sevoflurane. The appearance of similar EEG changes has also been documented with the use of isoflurane.

Isoflurane is a widely used inhalational agent in anaesthesia because it is relatively cheap, available and has relatively low blood-gas partition coefficient of 1.4 when compared to sevoflurane with blood gas solubility of 0.65. Agents with high blood gas partition coefficient are highly soluble with greater uptake by the pulmonary circulation but a slower increase in alveolar partial pressure [14]. This results into prolonged induction and recovery from anaesthesia. Rapid recovery from sevoflurane anaesthesia because of its low blood gas solubility coefficient has been reported as one of the reasons for the high incidence of EA found with the use of this agent. The relative lower incidence of agitation observed with isoflurane in this study conforms to its high blood gas solubility when compared to sevoflurane resulting into gradual recovery from anaesthesia. Also compared ketofol TIVA in different ratios (1.5, 1:67 and 1:10) in children who underwent adenotonsillectomy and found that the lowest incidence of EA was found in the group that had ketofol ratio 1:10. The difference in the incidence of agitation reported by Biricik et al when compared to the incidence in the present study may be attributed to the type of surgery. Adenotonsillectomy has been reported to be associated with high incidence of emergence agitation compared to ophthalmic procedures because of the feeling of suffocation being experienced by these children post operatively [15]. Also, Low dose ketamine in combination with propofol (Ketofol ratio 1:10) is effective to lower incidence of EA as observed in this study because it ensured adequate post-operative sedation and analgesia with good recovery parameters.

The cut off point for the severity of EA in this study was PAED score of >15. The higher the PAED score the greater the intensity and severity of the agitation. Severe form of EA was found more in the isoflurane group when compared to the ketofol group as evidence by the highest PAED score seen in the isoflurane group. This is similar to the findings of Chandler and colleague [16] who also reported the highest PAED score with sevoflurane as compared to the propofol remifentanil group. Singh et al compared the incidence and intensity of EA following the use of sevoflurane (40%), desflurane (28%), and isoflurane (16%) in children and reported that there was no statistically significance difference in severity of EA in the three agents but isoflurane group had the least incidence of agitation [17]. This may be attributed to the high blood -gas solubility coefficient of isoflurane when compared to these agents.

The time of emergence from anaesthesia and extubation may be important to improve the operating room efficiency. Prolong

emergence and extubation time may decrease the rate of turnover of patients in the operating room. This may also negatively affect any positive effect that would have been gained from rapid emergence from the effect of the anaesthetic agent. The emergence time was found to be non-significantly higher in ketofol group, 5.9 (3.1) than in isoflurane group 5.1(4.2). Contrary to this, [18] reported a longer emergence time of 8.2 with ketofol (ratio 1:4) TIVA in adult patients undergoing short elective procedures. The concentration of ketamine in combination with propofol (ratio 1:10) used in this study achieved a faster emergence that is comparable to the time of emergence from isoflurane.

The extubating time in ketofol group, 7.6 (3.1) was none significantly longer than in isoflurane group, 6.8 (4.4). The sedative effect of both propofol and ketamine may be the reason for this finding. Similar to this observation, [19] in a systematic review and meta-analysis of TIVA with propofol versus inhalational agent reported a non-clinically relevant longer time to extubation in propofol when compared to inhalational agent. Also reported the extubation time with ketofol TIVA (ratio 1:10) to be 254.3 ± 92.7 s which is not so much different from the extubation time observed with the ketofol group in this study. The slight difference may be due to procedure related factors. However, reported a longer extubation time of 9.8 minutes with ketofol (ratio 1:4) when compared to the finding in this study with ketofol (ratio 1:10). The high concentration of ketamine in combination with propofol may prolong the emergence and extubating time.

The participants in the Ketofol group experienced a non-statistically significant longer recovery time when compared to the Isoflurane group. This may be attributed to the hypnotic, sedative and analgesic effect of the intravenous anaesthetic agent. Which result into slower recovery from anaeshesia. Rapid wash out of the inhalational agent from the alveolar and central nervous system explain the shorter recovery time observed with the use of the inhalational agents. However, the recovery time reported with ketofol is similar to what was observed in the ketofol group in this study because the same dosage of ketofol was used. When patient stay longer than usual in the recovery room, there could be possibility of increasing nursing care during this period, this can have a significant impact in improving the efficiency and turnover rate per day of the operating suite.

CONCLUSION

The results obtained from this study on emergence agitation in children undergoing cataract extraction with the use of Ketofol and Isoflurane shows that the Ketofol group had a reduced incidence and severity of EA when compared with isoflurane. This was as a result of the combined sedating and analgesic effect of ketofol. The patient in the ketofol group also had a better recovery profile than the Isoflurane group.

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