Evaluation of Different Concentrations of Ketofol as a Sedative in Mastoid Exploration Performed under Local Anaesthesia

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ABSTRACT

BACKGROUND

Ketofol analgesia is considered a safe and useful technique as an alternative to general anaesthesia. The present study aimed to evaluate the use of "ketofol" as sedative in mastoid exploration performed under local anaesthesia.

METHODS

100 ASA grade I and II physical status patients aged 15 to 60 years were divided in to four equal groups of 25 patients each. Group I – Propofol / ketamine (2:1) infusion @ 2.5 mg / Kg / hr.; Group II – Propofol / ketamine (2:1) infusion @ 1.5 mg / Kg / hr.; Group III – Propofol / ketamine (3:1) infusion @ 2.5 mg / Kg / hr.; Group IV – Propofol / ketamine (3:1) infusion @ 1.5 mg / Kg / hr.

RESULTS

There was significant decrease in BP from baseline in all groups after induction. Significant hypotension was noted in one patient of group 3 (4 %) which was corrected by IV RL infusion (10 mg / kg). Difference between group III and others was insignificant. All patients had decrease in HR from baseline, maximum decrease in group II ($p<0.05$) but no patient had severe bradycardia requiring any intervention. After induction, all groups displayed marginal increase in $ETCO_2$, RR and SPO_2, all changes from baseline were statistically insignificant. None of the patients had hypoxia / excessive salivation.

CONCLUSIONS

Propofol in a concentration of 3:1 @ 2.5 mg / Kg / hr. provides titrable and predictable sedation with least consumption of propofol and ketamine and had minimum adverse effects.

KEYWORDS

Ketofol, Mastoid Exploration, Analgesia

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BACKGROUND

Procedural sedation is a minimally depressed level of consciousness that retains the patient's ability to maintain airways independently and continuously.[1] Various pharmacological agents are used in procedural sedation like sedatives (benzodiazepine), analgesics (opioids) and systemic anaesthetic agents.[2] Propofol is a short acting IV anaesthetic agent used for induction and maintenance of general anaesthesia for adults and children. It is also used for sedation for intubated and mechanically ventilated patients in ICU and in procedures like colonoscopy. But it does not provide any analgesia[3]. Ketamine is a NMDA receptor antagonist. It is a good analgesic and induces a state of dissociative anaesthesia.[4] Ketamine and propofol have been studied extensively either independently or with other agents.[5,6,7,8] But very limited studies are available on the combination of ketamine and propofol. Ketofol is a combination of ketamine and Propofol loaded in same syringe. Ketamine and propofol are physically compatible for one hour at 23 degree Celsius.[9] It has been used for various gynecological, ophthalmological and cardiovascular procedures in all age groups. The opposing haemodynamic and respiratory effects of each drugs increases both safety and efficacy of drugs and allows the reduction in dose of propofol required in achieving sedation. Ketofol has been used for procedural sedation and anaesthesia but the literature is limited.[10,11,12,13] In our study we evaluated different concentrations of Ketofol in mastoid surgeries regarding changes in hemodynamics, emergence phenomenon, recovery time, dose and adverse effects. Our aim is to find out the best possible concentration of ketofol and optimal rate at which desired sedation can be titrated to get the maximum benefit and minimum side effects.

METHODS

A randomized controlled study was conducted on 100 ASA grade I and II patients aged 15 to 60 years after approval of hospital ethical committee. Patients allergic to propofol / ketamine, history of hypertension, CAD, sleep apnoea and airway problems (macroglossia, obesity) were excluded from the study. Patients were randomized in four equal groups each of 25 patients undergoing mastoid exploration as follows-

Group I - Propofol / ketamine (2:1) infusion @2.5 mg / Kg / hr.
Group II - Propofol / ketamine (2:1) infusion @1.5 mg / Kg / hr.
Group III - Propofol / ketamine (3:1) infusion @2.5 mg / Kg / hr.
Group IV - Propofol / ketamine (3:1) infusion @1.5 mg / Kg / hr.

Pre anaesthetic check-up was done to evaluate if patients fulfil all the criteria of study and fasting instructions.

An intravenous line was secured with 18G cannula. Base line parameter like NIBP, HR, SPO2 and ECG were recorded. All patients were induced with propofol 1 mg / kg by a preloaded syringe followed by infusion of Ketofol with a syringe pump at the recommended rate. Ketofol (2:1) infusion was made by mixing 300 mg propofol (30 mL of 10% propofol) with 150 mg of ketamine (15 mL of 10 mg / mL) in total 45 mL of infusion in 50 mL of syringe that was containing 6.7 mg / mL of propofol and 3.3 mg / mL of ketamine. In group I infusion was started @ 2.5 mg / Kg / hr. In group II infusion rate was set at 1.5 mg / Kg / hr. Ketofol (3:1) infusion was made by mixing 300 mg propofol (30 mL of 10% propofol) with 100 mg of ketamine (10 mL of 10 mg / mL of ketamine) in total 40 mL of infusion in 50 mL of syringe. It contained 7.5 mg / mL of propofol and 2.5 mg / mL of ketamine. In group III infusion was started at 2.5 mg / Kg / hr. and in group IV infusion was started at 1.5 mg / kg / hr. After induction, surgeon was asked to infiltrate with local anaesthetic agents containing 2% lignocaine with 1: 100000 adrenaline and surgery was started.

During the procedure, patient's respiration was supplemented with oxygen by nasal prongs and ETCO2 sampling line was fixed under the drapes. Infusion rate was readjusted in case of pain or side effects like hypertension. Increments and decrements were done in stages of 0.5 mg / Kg / hr. till desired effect is achieved. All patients were monitored with NIBP, ECG, SPO2, HR, ETCO2 and RR. Monitoring started preoperatively and continues every 5 minutes intraoperatively and post-operatively at interval of 30 minutes for 3 hours and then 2 hourly till 12 hours. An intraoperative decrease in arterial blood pressure and heart rate of >15% of preoperative value was considered as hypotension or bradycardia and was treated with rapid infusion of Ringer lactate 10 mL / kg and atropine 0.6 mg respectively. SPO2 of <95% was taken as fall in saturation and loss of respiratory efforts for more than 20 sec is defined as apnoea. Complaints of pain / discomfort were treated by incremental increase in infusion rate. Drug infusion was stopped at the end of surgery and total drug requirement was noted. Patient was shifted to recovery when Aldrete score of 9-10 was confirmed. Intraoperative untoward events like need for intubation, conversion to GA, any incidence of PONV and other side effects (e.g. hallucination, pain and agitation) were recorded.

Time of awakening after stoppage of infusion was noted. Patients were discharged when they had stable vital signs, were oriented, able to ambulate unassisted and had no neurological deficit. Discharge time was determined from the time the study drug infusion was discontinued. Outdoor patients were given written discharge instruction regarding post-operative precautions, analgesia and whom to contact in case of emergency.

The data was analysed using the software SPSS 18 for windows. Appropriate univariate and bivariate analysis were carried out using the students T test for the continuous variable (age) and two failed fisher exact test or chi square (x^2) test for categorical variables. The comparison between four groups were done using ANOVA followed by Bonferroni post hoc test to multiple comparisons. The pain faces scores were compared using Kruskal Wallis test, a non-parametric

analog of ANOVA. All means are expressed as mean standard deviation.

RESULTS

		Group I	Group II	Group III	Group IV	P Value
Age (Years)		32.1 ± 11.1	35.4 ± 11.3	34.8 ± 12.8	35.4 ± 12.2	P > 0.05
Weight		56.9 ± 6.5	53.2 ± 6.3	54.1 ± 6.7	50.0 ± 6.7	P > 0.05
ASA Grade	I	20 (80 %)	21 (84 %)	20 (83.3 %)	20 (83.3 %)	P > 0.05
	II	5 (20.0 %)	4 (16.0 %)	4 (16.7 %)	4 (16.7 %)	
Duration of Surgery (in Hours)		2.4	2.35	2.5	2.3	P > 0.05

Table 1. Demographic Profile of Patients

p<0.05 was Considered as Significant., Demographic Characteristics of the Patients.

There were no significant differences among patients in all four groups regarding Age, Sex, weight, ASA Physical status and duration of Ketofol infusion (Table 1). One patient was excluded from Group III due to non-cooperation and one from Group IV due to inadequate pain score and pain relief and required intubation.

Preinduction Ramsay sedation score (RSS) was one i.e. awake and anxious in all patients irrespective of groups, so statistically insignificant. Post induction RSS score was similar in all the groups ($p > 0.05$). Mean sedation score was 4.41 ± 0.38 (Group I), 3.72 ± 0.12 (Group II), 4.61 ± 0.24 (Group III) and 3.91 ± 0.26 (Group IV) as show in table 2. It has been observed clinically that sedation was best maintained in group III. Patients of Group II and IV were under sedated and required either bolus of Propofol or increases in rate of infusion in some patients in group IV. Even one patient in group IV was excluded because he required intubation due to inadequate sedation.

	Group 1	Group 2	Group 3	Group 4
Preinduction Ramsay	1.00 ± 0.0	1.00 ± 0.0	1.00 ± 0.0	1.00 ± 0.0
Mean Ramsay Score	4.41 ± 0.38	3.72 ± 0.12	4.66 ± 0.24	3.91 ± 0.26
Preinduction Face Score	0.00 ± 0.0	0.00 ± 0.0	0.00 ± 0.0	0.00 ± 0.0
Mean Face Score	0.1014 ± 0.17385	0.2047 ± 0.25778	0.0857 ± 0.14112	0.78241 ± 0.39512

Table 2. Sedation Score and Pain Face Score of Patients in Different Groups

	Group 1	Group 2	Group 3	Group 4
Rate of consumption of propofol (mg / Kg / hr.)	2.89	1.90	2.61	1.82
Rate of infusion of ketamine (mg / Kg / hr.)	1.09	0.72	0.75	0.46
Mean Aldrete Score (0 min)	8.6 ± 0.5	8.6 ± 0.5	8.58 ± 0.5	8.75 ± 0.442
Aldrete Score (15 min.)	9.6 ± 0.5	9.76 ± 0.5	10.0 ± 0.0	10 ± 0.0

Table 3. Consumption in Various Groups / Recovery Time

Before induction, all patients were pain free as measured by pain faces score no statistically significant difference ($p > 0.05$). Mean pain score throughout the procedure were 0.10,0.20, 0.08 and 0.78 in groups I, II, III and IV respectively (Table 2) which was statistically significant in group I, II and IV and insignificant in group III, when compared with baseline pain score. Clinical observations also showed that patients in group III were most comfortable and group IV patients had maximum intraoperative pain.

Consumption of Propofol was maximum in group I@ 2.89 mg / Kg / hr. followed by group III @ 2.6 / mg / Kg / hr. Also, ketamine consumption was more in group I @ 1.19 mg / Kg / hr. followed by group III@ 0.75 mg / Kg / hr. Group II and IV had significantly less consumption of propofol and ketamine. Simultaneously sedation was inadequate in group 2 and 4 with higher pain scores.

Postoperative discharge criteria were assessed using Aldrete score on scale 0 to 10. The mean score at the end of procedure was 8.60, 8.60, 8.58, 8.75 in group I, II, III and IV respectively. Infusion of the study drug was stopped at last suture and Aldrete score assessment started when dressing had been completed. None of the patient had score of less than 8 at initial level. At 15 minutes, most of the patients had score of 10 in groups 2,3 and 4 except in group I which had score of 9 in almost all the patients. At 30 min all the patients had score of 10. The data was statistically significant (p value = 0.0001) clinically also patients in groups I had slow recovery. All the patients had average awakening time of 10-30 minutes, statistically insignificant.

There was significant decrease in BP from Baseline in all the groups after induction. Significant hypotension was noted in one patient of group 3 (4 %) corrected by iv RL infusion (10 mg / kg). Difference between group III and others was insignificant. All patients had decrease in HR from baseline, maximum decrease in group II ($p < 0.05$) but no patient had severe bradycardia requiring any intervention.

After induction all groups displayed marginal increase in $ETCO_2$, RR and SPO_2, all changes from baseline were statistically insignificant. None of the patients had hypoxia / excessive salivation.

Complications

Two patients (8%) in group 4 had tongue fall following propofol boluses and required airway support by oral airway. 2 patients in group 4 and one patient in group 2 had pain and discomfort. 3 patients in group 1 (12%) and one patient in group 2 had nausea / vomiting. Three patients in group I (12 %) had emergence reaction in the form of hallucination. So it is clear that group I had highest drug consumption, maximum side effects and longest duration of discharge. Though group 2 and group IV had less drug consumption and early recovery, but sedation was inadequate and pain score was significantly higher. Group 3 had comparable drug consumption, best sedation, least pain score, fewer side effects and stable haemodynamics and respiratory parameters.

DISCUSSION

Ketofol is used as a sedative to provide adequate level of sedation,[8] to minimize pain, anxiety, time to full recovery and adverse drug related events.[1,2] Combination of two agents appears to reduce the side effects of each medication

used alone and allow a rapid recovery rate.[12,14] In our studies, we compared the safety and efficacy of two different combination of ketofol each given at two different rates of delivery to assess which drug concentration given at what rate provides best level of procedure sedation. Our results suggest that combination of propofol and ketamine (3:1) @ 2.5 mg / Kg / hr. was most suitable in mastoid exploration as a sedative and analgesic. The results were consistent with the study reported by Badrinath et al.[15] They also reported that combination of ketamine and propofol (5:1) provides effective sedative / analgesic during monitored anaesthesia care. Induction with propofol always resulted in fall in Blood pressure which was mild and similar in all groups, however this returned to baseline on commencement of ketofol infusion. This was due to the fact that sympathomimetic action of Ketamine was effective in counteracting the hemodynamic depression of propofol. Studies by Aquad MT et al, Akin A et al, Furua et al also showed better hemodynamic stability by addition of ketamine with propofol.[14,16,17]

There was a trend for pulse rate to decrease after induction in all groups, but there was no profound bradycardia in any of the group. This contradicts Hui TW et al and Akin A et al who reported tachycardia due to ketofol induction.[16] All the patients had a good control on ventilation with slight variation in respiratory rate. Though end-tidal co_2 increased slightly after induction in all groups but respiration remained stable throughout the surgery. our observations are in agreement with Midhetal and Persson et al who reported that ketamine induced sympathoadrenal activation may account for improved ventilation, also arousal secondary to subjective side effects of ketamine (e.g. perceptual changes and anxiety may also contribute.[5,6]) Our study also confirm the reports of Frey et al and Rosendo Fetal, who concluded that coadministration of small doses of ketamine attenuates propofol induced hypoventilation.[15,18]

Two patients (8 %) in group 4 had tongue fall and airway obstruction after propofol bolus to combat low sedation which required oropharyngeal airway insertion. None of the patient had apnoea, hypoxia and excessive salivation in all the groups. Clinically significant psychomimetic effect was noted in the large dose ketamine group (Group 1). This could be a dose dependent interaction of the excitatory anaesthetic ketamine with a pure central nervous system depressant such as propofol.[7,8,11] There was no post procedural psychomimetic symptoms in groups II, III and IV. Our results are in agree with those of Nagrta et al and Mortero et al as they suggested that ketamine in sedative doses is associated with EEG activation.[19,20] Further small doses ketamine increases thalamic sensory output and arousal. Sedative effects of propofol may be partially antagonized by the arousal effects of ketamine.[19,20]

Mohamed Daabir et al had studied assessment of different concentration of ketofol in which patients received an infusion of a solution containing combination of propofol, ketamine 1:1 (Group 1) or 4:1 (Group 2). They found that there was an increase in postop nausea, psychomimetic effects and delay in discharge time in the largest ketamine dosage (Group I).[12] Our results coincide with the above study as 3 patients in group I and only one patient in group 2 had nausea / vomiting having larger ketamine concentration in ketofol (2:1). On the other hand, none of the patients in group 3 or Group 4 had nausea / vomiting having lower ketamine concentration in ketofol (3:1).

Frey Ketal and Rosendo F et al have concluded in their study that low dose ketamine in combination with propofol has resulted in better postoperative recovery in patients undergoing procedural sedation.[18] We also concluded that ketofol (3:1) has better recovery profile with average awakening time of 15-30 min and average time of ambulation was 1-2 hours. Ketofol (3:1) @ 2.5 mg / Kg / hr. provides excellent level of sedation and analgesia with good hemodynamic stability, airway protection and least side effects with early recovery in even prolonged infusion up to 3 hours.

CONCLUSIONS

Ketofol, used in a concentration of 3:1 @ 2.5 mg / Kg / hr. provides titrable and predictable procedural sedation with least / optimum consumption of propofol and ketamine, with minimum adverse effects for long surgical procedures like mastoid exploration. This combination is also safe during such procedures as it provides best haemodynamic stability with least respiratory depression.

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