ORIGINAL ARTICLE

Thiopental versus ketofol in paediatric sedation for magnetic resonance imaging: A randomized trial

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Abstract

Objective: To compare the efficiency of intravenous thiopental against intravenous ketamine-propofol combination in paediatric sedation for magnetic resonance imaging.

Methods: This prospective study was conducted at Ondokuz Mayis University Hospital, Samsun, Turkey, from July 1, 2014, to January 1, 2015, and comprised children aged 1 month to 12 years undergoing elective magnetic resonance imaging who were randomly assigned to two equal groups. Group I received thiopental 3 mg/kg intravenously followed by an additional dose of thiopental 1 mg/kg to achieve a Ramsay sedation score of 4. Group II received ketofol, a 1:1 mixture of ketamine 10 mg/mL and propofol 10 mg/mL, in a single syringe intravenously at a dose of 0.5 mg/kg at 1 minute intervals and titrated to reach a Ramsay sedation score of 4. The groups were compared for total drug dose, time to sedation, recovery time, total sedation time, and adverse effects. Data was analysed using SPSS 22.

Results: There were 120 children in the study; 60(50%) in each group. The time to sedation was significantly longer with ketofol than thiopental ($p<0.01$). The mean recovery time was significantly shorter with thiopental than with ketofol ($p<0.01$). Total sedation time was significantly longer with ketofol than thiopental ($p<0.01$). Overall, 17(28.3%) ketofol patients had adverse events, whereas no thiopental patients had adverse events ($p<0.0001$).

Conclusion: Thiopental had a comparable effectiveness with shorter anaesthesia inductions and recovery times than ketofol. Intravenous thiopental can be an effective and safe alternative drug in sedating children undergoing magnetic resonance imaging.

Keywords: Thiopental, Ketamine, Propofol, Paediatric, Magnetic resonance imaging. (JPMA 67: 247; 2017)

Introduction

Magnetic resonance imaging (MRI) is a widely used radiology technique with its unique noisy environment and a narrow pipe like appearance. However, it is very difficult for a child to remain motionless to avoid movement artefact, and get a qualified image. Therefore children frequently require sedation or general anaesthesia for extended periods to maintain immobility and to attenuate anxiety while undergoing MRI.[1] Especially with limited access to a child lying down inside the electromagnetic coil, the most appropriate sedative drug/drugs need to be selected for patient's safety.[2]

Among a variety of sedative drugs being used for sedation, propofol, a sedative-hypnotic agent, is widely used with its rapid effect, short recovery time, and antiemetic effect. However, propofol alone may not maintain immobility of the child, therefore repeated doses are required which can result in respiratory depressant effect, and decrease in protective airway reflexes.[3] While a single agent may not offer all of the desired goals, combinations of various drugs may achieve the desired results.[4] The intravenous (IV) administration of low dose ketamine prior to propofol induction or infusion can maintain haemodynamic, respiratory stability with the same recovery time and MRI quality when propofol alone in used.[5]

The barbiturates have been used safely for over 30 years. IV pentobarbital, rectal methohexital and thiopental are the barbiturates that have been studied for procedural sedation. Thiopental can produce effective sedation within 1 min, and has a rapid clinical recovery (about 15 min) when administered intravenously.[6] With its adequate sedation, faster recovery, and lower rate of bradycardia and desaturation, IV thiopental is suggested to be reconsidered for sedation in radio-diagnostic procedures.[7] Although using rectal thiopental for sedation of children in MRI is common, in literature there is very little knowledge about its IV use. Therefore, we hypothesised that IV thiopental and ketofol would be alternatives for sedation in paediatric MRIs. The current study, as such, was planned to investigate the effectiveness and safety of ketofol and IV thiopental, and

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to compare the two.

Subjects and Methods

This prospective study was conducted at Ondokuz Mayis University Hospital, Samsun, Turkey, from July 1, 2014, to January 1, 2015, after approval by the institutional ethics committee and receipt of written informed consent from the subjects and/or their parents. The sample size was calculated assuming a statistical power of 99.7% and an alpha of 5%.[8] Children undergoing elective MRIs equivalent of American Society of Anaesthesiologists (ASA) status I/II, and aged 1 month to 12 years were randomly assigned to one of two groups. Patients in ASA III/IV status, who had a current upper respiratory infection, congenital heart disease, who had a history of asthma, porfyria, hyperactivity disorder, allergy to egg and study drugs, who had a known or potential risk to difficult airway (e.g cranio-facial anomalies, micrognathia, adeno-tonsillar hypertrophy) were excluded.

After maintaining a peripheral catheter, group I received thiopental 3 mg/kg intravenously followed by an additional dose of thiopental 1 mg/kg to achieve the targeted level of a Ramsay sedation score of 4. Group II received ketofol, a 1:1 mixture of ketamine 10 mg/mL and propofol 10 mg/mL, in a single syringe intravenously at a dose of 0.5 mg/kg at 1-min intervals and titrated to reach a Ramsay sedation score of 4.[9] The target level of sedation was determined as Ramsey sedation score of 4 because this level of sedation is accepted as the minimum level needed to complete the imaging successfully.[10] All patients breathed spontaneously through an oxygen facemask without an artificial airway. The patients were monitored with pulse oximetry, capnography. Heart rate, respiratory rate, peripheral oxygen saturation, end-tidal carbon di oxide (CO2) were recorded at 5-minute intervals throughout sedation. In case of peripheral capillary oxygen saturation (SPO2) level decreasing below 93% or no respiratory effort was observed for 30s, the procedure was planned to be interrupted and the patient was taken out of the MRI tunnel. The function of the anaesthesiologist was to insert an oral/nasal artificial airway, place a shoulder roll, or tape the chin to manage airway obstruction. After completion of the imaging, the patients were transferred to the recovery room near the MRI unit. Children were discharged if they met standardised discharge criteria of stable airway patency, a return to pre-MRI level of vital signs and consciousness, and a minimum Aldrete score of 8 or greater.[10,11] The data of age, weight, total drug dose, time to sedation, recovery time, total sedation time, and adverse effects (i.e., episodes of apnoea, nausea, vomiting, paradoxical reactions) were recorded and the groups were compared accordingly.

Data was analysed using SPSS 22. Shapiro-Wilk test was used to analyse normal distribution assumptions of the quantitative outcomes. Normally distributed ordinal and continuous variables were expressed as mean ± standard deviation (SD) and intergroup variables were compared with independent t-test. Categorical data was analysed with chi-square test. Ordinal and continuous variables that were not normally distributed were expressed as median and interquartile ranges (IQR), and intergroup variables were analysed with MannWhitney U-test. Differences between the groups were considered statistically significant at $p<0.05$.

Results

There were 120 children in the study; 60(50%) in each group. There were not statistical significant intergroup differences with respect to age, gender, weight, ASA status, or the length of the procedure ($p>0.05$ each). Sedation was effective in all patients. All MRI scans were completed without any artificial airway. The mean total doses were 4.9±0.9 mg/kg for thiopental and 2.6±0.8 mg/kg for ketofol. Patients in ketofol group needed longer time to sedation (2.3±0.5 min versus 0.9±0.1 min; $p<0.0001$) than the children in thiopental group. Similarly, the mean recovery time was significantly shorter with thiopental than with ketofol (9.4±2.6 vs. 20.4±4 minutes; $p<0.0001$). Total sedation time was significantly longer with ketofol than with thiopental (36.2±6.6 vs. 24.2±5; $p<0.0001$). The median supplemental dose required to keep children in Ramsay sedation score of 4 was more in

Table-1: Demographic and sedation data of groups.

	Thiopental (n = 60)	Ketofol (n = 60)	P value
Demographic			
Gender*			
M	32 (53)	31 (52)	0.85
F	28 (47)	29 (48)	
ASA*			
I	19 (32)	23 (38)	0.44
II	41 (68)	37 (62)	
Age (y)**	4.5±3.2	4.3±2.5	0.80
Weight (kg)**	17±9.4	17.6±8.1	0.74
Characteristic			
Length of procedure**	14.1±4.1	14.7±4.9	0.46
Total dose (mg/kg)**	4.9±0.9	2.6±0.8	0.00
Time to sedation (min)**	0.9±0.1	2.3±0.5	0.00
Time to recovery (min)**	9.4±2.6	20.4±4.0	0.00
Total sedation time (min)**	24.2±5.0	36.2±6.6	0.00
Supplemental dose***	1 (0-2)	2 (1-4)	0.00

ASA: American Society of Anaesthesiologists
* Data in parentheses are percentage.
** Data are the mean ± SD.
*** Data in parentheses are ranges.

Table-2: Heart rate and adverse effect in groups.

	Thiopental (n = 60)	Ketofol (n = 60)	P value
Heart rate (per minute)	101.9 ± 16.1	102.46 ± 13.5	0.83
Adverse events			
Oxygen desaturation	0	0	
Vomiting	0	0	
Transient diplopia	0	2 (3.3%)	
Unpleasant emergence reactions	0	5 (8.3%)	
Nystagmus	0	10 (16.6%)	

ketofol group (2 (IQR: 1-4) than thiopental group (1 (IQR: 0-2) (p<0.0001) (Table-1). The mean heart rate was 101.9 ± 16.1 for thiopental and 102.46 ± 13.5 for ketofol (p=0.83).

Overall, 17(28.3%) subjects had adverse events in the ketofol group, whereas none in the thiopental group had any adverse events (p<0.0001). Of the 17 ketofol adverse events, 2(3.3%) had transient diplopia, 5(8.3%) had unpleasant emergence reactions, and 10(16.6%) had nystagmus. None of the patients had vomiting or oxygen desaturation (Table-2).

Discussion

The study investigated the effectiveness and safety of ketofol and thiopental, then compared them with each other in paediatric MRIs. Results demonstrated that both ketofol and thiopental provided effective and safe sedation, but thiopental had a comparable effectiveness with shorter anaesthesia inductions and recovery times than ketofol (1:1).

Ketamine is a dissociative sedative with analgesic and amnestic effect, and commonly used for procedural sedation and analgesia in children.[12] It preserves spontaneous respirations and protective airway reflexes as advantage. Besides, it can produce emesis, and result in long recovery time as a disadvantage. However, it is relatively contraindicated for radiographic imagining because of typical random movements caused by dissociation.[13]

The usage of ketamine-propofol combination (ketofol) was first described in 1990s with observation of decreased emergence reactions after propofol use prior to ketamine administration.[13] This combination has been used in a variety of settings during burn dressing change, interventional radiology procedures and procedural sedation in emergency department.[14-16] However, we could find no studies about single syringe ketamine propofol combination used in paediatric MRIs. The studies about ketofol sedation have all shown to benefit cardiovascular stability and airway preservation in procedural sedation with a counterbalance of each drug's effect.[4] In our study we also observed ketofol as a cardiovascular stable and effective sedative in paediatric MRIs. Our patients' mean heart rates were at baseline during sedation and recovery periods. We usually do not use routinely non-invasive blood pressure monitor because the intermittent inflation of the blood pressure cuff may disturb lightly sedated patients, and may cause patients to move and disrupt the MRI procedure. The combination of propofol and ketamine can be used either in separate syringes or in a single syringe. Because the mechanism, kinetics and action duration of two drugs are different and it has been proved that fixed doses of ketamine and propofol can produce effective sedation, same-syringe ketamine-propofol use can be a rational choice.[12] Tomatir et al. investigated the effect of low dose (0.5 mg/kg) ketamine just before propofol anaesthesia in paediatric MRIs. After ketamine administration they gave 1.5 mg.kg propofol intravenously and started propofol infusion at a rate of 75 μg.kg-1.min. Two of 23 patients required chin lift and airway placement, 5 children moved, and one child had excessive secretion. All patients experienced significant decrease in heart rate. In the present study our dose for ketofol (each millilitre contains 5 mg each of ketamine and propofol) was also 0.5 mg.kg, but with this mixture in a single syringe we used less dose of ketamine and propofol. This can explain why our patients did not require chin lift and airway placement. In a prospective case series of paediatric procedural sedation in emergency department, Andolfatto et al used single-syringe ketamine-propofol combination, and they reported highly effective and staff-satisfied sedation with short recovery times and few adverse effects. They concluded that ketofol can be an effective paediatric procedural sedation option.[12] We also found ketofol as an effective sedative in paediatric MRIs. One may argue that using ketamine in combination with propofol is not necessary for a painless radiological procedure, but as ketamine has been used in procedural sedation because of its analgesic effect, it can also be used in a painless procedure because of its respiratory stability. The benefits of ketofol like cardiovascular-respiratory stability, and antiemetic properties make this combination reasonable choice not only in painful but also in painless procedures.[13] Ketofol use for painless procedure was also reported for laryngeal mask airway (LMA) insertion in elderly patients. In a study Erdogan et al. investigated the effect of ketofol on LMA insertion condition and haemodynamics, and compared it with propofol alone. They found same insertion conditions, but lower ephedrine dose requirement and apnoea duration than

propofol. They did not observe any excessive secretion in ketofol group. They concluded that ketofol was a good choice for elderly patient while inserting LMA.[17] In the present study we also did not observe any excessive secretions in our patients, but they had some other adverse events like injection pain, diplopia, unpleasant emergence reaction, and nystagmus. In a study of ketamine-propofol combination sedation in paediatric emergency care, Ghazala et al. also observed injection pain, unpleasant emergence reaction in fracture reduction of paediatric patients. In another study Silva et al used ketofol for procedural sedation in children undergoing bone marrow aspiration, 2 of 20 patients had transient injection pain and diplopia. No patients required airway interventions. The recovery time and total sedation time in our study were in line with this study (20.4 ± 4.0, 36.2 ± 6.6 min respectively).

While we observed an effective and safe sedation with ketofol, we also found thiopental effective and safe. Among the sedatives used for procedural sedation, IV pentobarbital, rectal methohexital and thiopental are the most extensively studied barbiturates.[18] There are a few studies about the use of rectal thiopental and IV thiopental for paediatric MRIs in literature.[7,19-22] In a prospective study about sedation for children with metachromatic leukodystrophy undergoing MRI, Mattioli et al. used IV thiopental in patients up to 3 years of age. In patients over 3 years of age, sedation was induced with propofol. Their IV thiopental induction and rescue bolus dose were 5 mg.kg - 2.5 mg.kg respectively. They found thiopental as safe and effective as propofol in their study. In the present study our induction dose was 3 mg/kg intravenously, and the additional dose to achieve adequate sedation was 1 mg/kg, but the mean total doses were (4.9 ± 0.9 mg/kg) similar with the study of Mattioli et al.[21] We used thiopental not only in patients up to but also over 3 years old, and we found thiopental as an effective and safe drug for sedation in MRI in all patients. Similarly, in another study, Hasani et al. compared the efficiency and safety of thiopental with propofol in 67 children undergoing MRI. They found thiopental effective and safe with the findings of shorter total sedation time (26.9 minutes vs. 55 minutes respectively), and lower side effects than with the findings of propofol.[7] In our study the total sedation time for thiopental was consistent with the study of Hasani et al. In a study comparing sedative effects of midazolam-ketamine combination and thiopental in children undergoing MRI, Selcuk et al. used same induction, and rescue bolus dose like us, and they found shorter total sedation and recovery time with thiopental. They suggested thiopental as a safe alternative to midazolam-ketamine combination for paediatric MRIs.[22]

Our second target was to compare the efficiency and safety of ketofol with thiopental. Since we found both drugs effective and safe, the total dose, time to sedation, supplemental dose needed, recovery time, and total sedation time were significantly lower with thiopental when compared with ketofol. Additionally, we also observed no complication in thiopental group consistent with the other studies with this drug.[7,22] This kind of significant difference can be explained maybe with pharmacokinetics of these drugs. While propofol is ultrashort acting drug, ketamine has longer action of duration than propofol which can result in accumulation of ketamine relative to propofol.[4] The longer recovery time, and total sedation time in ketofol group can be related with this kind of accumulation. This can also explain the adverse effects that we observed with ketofol. Because all of them were the side effects of ketamine except injection pain.

The limitation of this study is that it was not a double-blinded study. In studies that the drug administrator is not blinded to the treatment given to patient, some personal subjective biases may affect the reporting and evaluating data consciously or unconsciously.[23] Another limitation was the used ratio of ketamine-propofol mixture (1:1). In a randomized double-blinded study comparing adverse effect of 1:1 propofol-ketamine mixture with a ratio of 4:1, Miner et al. found same frequency of airway and respiratory adverse events, but they observed more recovery agitation in the 1:1 group.[24] Therefore, further research with different ratios of the ketamine-propofol mixture is required to determine its efficacy, safety and applicability.

Conclusion

IV thiopental compared with ketofol (1:1) had a comparable effectiveness with shorter anaesthesia inductions and recovery times. We suggest that IV thiopental can be an effective and safe alternative drug in the sedation of children undergoing MRI. Further studies are needed to compare effectiveness of IV thiopental with other commonly used anaesthetics in paediatric MRIs.

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