Original Article

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Comparing the effect of sedation with two different ratios of Ketofol on amnesia in children with acute leukemia who are candidate for intrathecal injection of chemotherapy drugs

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Abstract

Background: Ketamine increases blood pressure and heart rate. Propofol is an anesthetic drug with rapid recovery, but it causes respiratory depression, low heart rate and low blood pressure. Combination of ketamine and propofol provides sedation, analgesia, and rapid recovery with hemodynamic stability and minimal respiratory depression. There have been a few studies about the effect of different concentrations of ketofol on amnesia in the children with leukemia undergoing intrathecal injection of chemotherapy drugs, so this study investigated the effect of two concentrations of ketofol (1/5 with midazolam and 1/10) on amnesia in these patients.

Materials and Methods: This randomized, double blinded study was conducted on 64 ALL children aged between 5 to 12 years old and referred to Shahid Sadoughi hospital for intrathecal chemotherapy from July 2016 up to September 2016. The patients received titrated injection of a solution containing combination of one part of ketamine and ten parts of propofol (1:10) (group I) or one part of ketamine and five parts of propofol (1: 5) with midazolam(0.5mg) (group II) to sedate at the fifth level of Ramsay Sedation Scale. Amnesia was evaluated using visual recognition of posters and recall of specific events. Drug side effects such as nausea, vomiting, hallucination, allergies, dizziness, cough, and apnea were also evaluated in the patients.

Results: No significant difference between two groups was found regarding age and weight (p- value=0.625, p-value=0.830). Running Chi-square revealed no statistically different between groups in terms of posters recognition and recall of specific events. In terms of drug side effects, two groups were similar but for hallucination that was higher in group (p- value = 0.043).

Conclusion: The results showed that ketofol 1/10 is superior in comparison to ketofol 1/5 with midazolam (0.5 mg) according to less side effects and similarity in amnesia induction.

Key Words: Amnesia, Chemotherapy, Intrathecal Injection, Ketofol, Leukemia, Sedation

Introduction

Amnesia is defined as a loss of memory-access to events that happened, or information that was learned, before an injury or the onset of a disease (1). Memory loss can be occurred by use of sedative and hypnotic sedative drugs depending on the depth of anesthesia and the used doses. Anaesthesia is a temporary induced state, including analgesia (relief from or prevention of pain), paralysis (muscle relaxation), amnesia (loss of memory), and unconsciousness. There are two main types of amnesia; namely, anterograde amnesia which is the more common type occures when the ability to memorize new things is impaired or lost since data does not transfer successfully from the conscious short-term memory into permanent long-term memory and retrograde amnesia happens when a person's pre-existing memories are mised to conscious recollection, beyond an ordinary degree of forgetfulness, even though they may be able to memorize new things that happen after the onset of amnesia. Sometimes both these types of amnesia may occur together which is

called total or global amnesia. In anesthesia, it is tried to achieve anterograde amnesia memory temporarily using various drugs; including propofol, ketamine, midazolam, fentanyl, alfentanil, remifentanil, or a combination of them, like ketofel. Considering the growing incidence of pediatric malignancies, including hematologic malignancies and the psychological adverse side effects of treatment measures such as chemotherapy on pediatric, amnesia induction and oblivion of these memories are very important. Due to short time of these measures, it is necessary to use medications or combination of them to not only remove anxiety effectively and create amnesia but also have a short-acting medication which does not result in sleepiness, agitation or significant complications for patients after chemotherapy completion. Selecting the appropriate medication or combination of them depends on the place (ward or the operating room), patients 'age, and the kind of admission (as outpatients or inpatients).

Propofol is a generalized intravenous anesthetic which is used in lower doses as sedation and hypnosis (2). Propofol has various benefits, including anxiolysis, anticonvulsant activity, antiemesis, and the ability to reduce intracranial hypertension (3, 4). Since propofol is not apain medication, opioids such as morphine may also be used (5). The most important advantage of propofol is its rapid onset and offset of action. This behavior of a "rapid on, rapid off" feature, not available with the intravenous opiates or benzodiazepines, leads to the increasing popularity propofol. Since the onset of action after a single dose is rapid, and its effect brief (~ 10-15 minutes) because of high lipophilicity and central nervous system penetration, propofol is given merely by continuous infusion when used for sedation. Propofol, similar to other anesthetics, is a potent respiratory depressant, suppressing both the hypercarbic and hypoxemic drives of ventilation. This effect synergizes with that of other medications, and is dose-dependent. Because the propofol is mixed in a liquid involving soybean oil and egg lecithin,its use should be prohibited in soy-allergic and egg-allergic patients.

Ketamine is a phencyclidine derivative that maintains muscle tone and ensures air route reflexes, and sustains a stable respiratory status. In contrast to propofol, ketamine stimulates the sympathetic and does not cause cardiorespiratory depression. Its effects typically begin within five minutes when given by injection with the main effects lasting up to 20 minutes. In addition to analgesic and sedative effects, ketamine in combination with propofol can also cause anterograde amnesia results in prevention of undesirable memory negative behavioral effects after chemotherapy in patients. Common side effects of ketamine include nausea, vomiting, tachycardia, elevated blood pressure in the brain and eyes, psychological reactions(agitation, confusion, and hallucinations) (6,7, and 8).

Midazolam drug is of benzodiazepines class and enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor, leading to sedative,hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties. Midazolam can be administered by mouth, intravenously, by injection into a muscle, sprayed into the nose, or in the cheek (9, 10). Its side effects include sensitivity and acute narrow-angle glaucoma.

Considering the advantages and disadvantages of each of these drugs, the use of ketamine and profonol in combination (ketofol) and inside the same syringe can be an appropriate measure. The combination of these two drugs makes each dose reduced results in fewer side effects. The contrasting hemodynamic and respiratory effects of these two drugs accounts for the sympathetic nervous

system stimulation and blood pressure increase by ketamine and improvement of hemodynamic changes caused by propofol. Moreover, profonol reduced the ketamin-induced complication such as vomiting. Ketamine and propofol when combined together in a polypropylene syringes and kept at room temperature (23c) can be chemically stable for one hour. The effect of ketamine and propofol in the creation of amnesia in children has not been studied yet. Therefore, we decided to examine the combination of ketamine with propofol with two different ratios of 1: 5 and the 1: 10 in children with acute leukemia who are candidate for intrathecal injection of chemotherapy drugs.

Materials and Methods

Given that patients and residents were unaware of the injected drug, this study had a double-blind design. Informing the patients about the type of operation and sedative drugs and obtaining written consent, this randomized clinical trial was conducted on ALL children aged between 5 to 12 years old and referred to Shahid Sadoughi hospital for intrathecal chemotherapy from July 2016 up to September 2016. Children with a history of growth and development disorders, neurological disorders, history of seizures, memory disorders, mood disorders, allergy to ketamine or propofol, previous allergies to eggs or soy were excluded. No significant difference between two groups was found regarding age and weight (p-value=0.625, p- value=0.830) (Table 1).

Two groups were compared before conducting the study with respect to events and poster recalling and drug side effects. The results were analyzed running Chi-square and the findings are presented in Table II.

Patients were divided into two groups of 34 and 30 using table of random numbers. The purpose of sedation was achieving Ramsay score 5 according to Table III and 5 maintaining it to perform the desired procedure. For group 1, ketofol at the concentration of 1: 5 (1 mg ketamine plus 5 mg propofol) plus 0.5 mg of midazolam were administered. Group 2 received ketofol at the concentration of 1: 10 (1 mg ketamine plus 10 mg propofol). Drugs were prepared and encoded by anesthetic technicians. Then, anesthesia resident who was blinded about the study administered the drugs until the patient reach Ramsay score of 5 and during the procedure this amount of sedation was maintained. One minute after drug administration, 10 posters were displayed to the children. To assess the patient's memory and recalling the events, 5 events were considered: 1. placing Pulse Oximeter on the finger, 2.pouring Betadine on the waist, 3.the placement of the needle tip to desired location, 4. transferring the patient to the recovery, and 5. remembering a special sentence. These five events were related to the time when the child reached the depth of sedation that is Ramsay score of five. When children reached Aldrete score 9 to 10 (Table III), anterograde amnesia and recalling of posters and events were examined during an interview. That is, 10 posters were re-displayed to children and they were asked about the recalling of posters. In addition, children in both groups were questioned about the recalling of those 5 events. The obtained information was recorded by questionnaire and analyzed running SPSS (version 232). $P<0.005$ was considered as a statistically significant level. Ketamine used in this study was product of Rotex Media (Germany) and the propofol was produced by Claris Life Sciences Limited (India) which were prepared at the start of the project.

Results

A total of 64 patients were examined in this study (30 patients in group 1 received ketofol at the concentration of 1: 5 with midazolam and 34 patients in group 2 received ketofol at the concentration of 1:10).In the first group, thirteen patients were males and 17 females. In the second

group, 14 were males and 20 were females. The patients were compared in terms of age and the results are depicted in the Table III. Running Independent samples test revealed no significant difference between two groups regarding age (p- value=0.625). Two groups were compared with respect to events recalling and the results were analyzed running Chi-square and the findings are presented in Table IV. As it is clear from Table IV, no significant difference was found between two groups. Two groups were examined in terms of posters remembering and the summary of the results are demonstrated in the Table V. Based on Table V, no significant difference was found between two groups. Patients in both groups were compared in terms of drug side effects such as nausea, vomiting, hallucination, allergies, dizziness, cough, and apnea. The results are shown in Table VI. The difference between the two groups was not significant in terms of the side effects; namely, nausea, vomiting, dizziness, and coughing. In none of the groups allergies and apnea was observed. However, a significant difference was found between two groups regarding hallucination (p-value= 0.043).

Table I: Baseline information before conducting the study

Group		N	mean	P_VALUE
Age	**1**	30	7.70	0/666
	2	34	7.94	
Weight	**1**	30	22.00	0/830
	2	34	21.65	

Table II: Analytical results across the intervention and control groups

	Control group		Intervention group		P-value
	No	yes	No	yes	
Event 1	5(16.7%)	25(83.3%)	1 (2.9%)	33 (97.1%)	0.074
Event2	27(90%)	3(10%)	4(100%)	0	0.097
Event3	27(90%)	3(10%)	33(97.1%)	1 (2.9%)	0.260
Event4	29(96.7%)	1(3.3%)	33(97.1%)	1 (2.9%)	0.722
Event5	18(36.7%)	19(63.3%)	15(44.1%)	19(55.9%)	0.363
Poster1	4(13.3%)	26(86.7%	1(2.9%)	33(97.1%)	0.141
Poster2	2(6.7%)	28(93.3%)	3(8.8%)	31(91.2%)	0.560
Poster3	6(20%)	24(80%)	10(29.4%)	24(70.6%)	0.283
Poster4	7(23.3%)	23(76.7%)	6(17.6%)	28(82.4%)	0.399
Poster5	3(10%)	27(90%)	6(17.6%)	28(82.4%)	0.305
Poster6	0	30(100%)	2(5.9%)	32(94.1%)	0.278
Poster7	4(13.3%)	26(86.7%)	4(11.18%)	30(88.2%)	0.572
Poster8	4(13.3%)	26(86.7%)	4(11.18%)	30(88.2%)	0.572
Poster9	5(16.7%)	25(83.3%)	3(8.8%)	31(91.2%)	0.285
Poster10	2(16.7%)	28(93.3%)	2(5.9%)	32(94.1%)	0.644
Nausea	25(83.3%)	5(16.7%)	32(94.1%)	2(5.9%)	0.164
Vomiting	29(96.7%)	1(3.3%)	34(100%)	0	0.469
Hallucination	26(86.7%)	4(13.3%)	34(100%)	0	0.043
Allergies	30(100%)	0	34(100%)	0	1.000
Dizziness	29(96.7%)	1(3.3%)	32(94.1%)	2(5.9%)	0.548
Apnea	30(100%)	0	34(100%)	0	1.000
Cough	28(93.3%)	2(6.7%)	30(88.2%)	4(11.18%)	0.398
Hypotension	30(100%)	0	34(100%)	0	1.000

Table III: comparison of patients in terms of age

Group	number	mean	SD
Ketofol 1:5	30	7.70	2.261
Ketofol 1:10	34	7.97	2.139

Table IV: Comparison of two groups in terms of events remembering

incidence	Recalling		p- value
	Group 1	Group 2	
1. placing Pulse Oximeter on the finger	97.1%	83.3%	0.073
2.pouring Betadine on the waist	0.0%	10%	0.097
3.the placement of the needle tip to desired location	20.9%	10%	0.260
4. transferring the patient to the recovery	2.9%	3.3%	0.722
5. remembering a special sentence	55.9%	63.3%	0.363

Table V: Comparison of two groups in terms of poster remembering

poster recalling	Group		p- value
	Group 1	Group 2	
Poster1	97.1%	86.7%	0.141
Poster2	91.2%	93.3%	0.560
Poster3	70.6%	80%	0.564
Poster4	82.4%	76.7%	0.399
Poster5	82.4%	90%	0.305
Poster6	94.1%	100%	0.562
Poster7	88.2%	86.7%	0.572
Poster8	88.2%	86.7%	0.572
Poster9	91.2%	83.3%	0.285
Poster10	94.1%	93.3%	0.644

Table VI: comparison of two groups in terms of drug side effects

side effects	Group		p-value
	Group 1	Group 2	
nausea	5.9%	16.7%	0.164
vomiting	0.0%	3.3%	0.469
hallucination	0.0%	13.3%	0.043
allergies	None of the groups experienced allergy		
dizziness	5.9%	3.3%	0.548
apnea	None of the groups experienced allergy		
cough	11.8%	6.7%	0.398

Discussion

The goal of the sedation process is rendering conditions in which the patients experience minimum pain and restlessness and maximum of amnesia which results in the least side effects.

This study was attempted to compare the efficacy of two different concentrations of ketofol in order to achieve this goal. In this study, results showed that ketofol at the concentration of 1/10 in comparison with ketofol at the concentration of 1/5 in combination with midazolam (0.5 mg) induced the same level of amnesia in children with acute leukemia who are candidate for intrathecal injection of chemotherapy drugs. That is, no significant difference was found between two groups regarding the reminding of posters (10 posters) and events (5 events). Considering the drug side effects, no significant difference was found between groups but for hallucination which was higher in the second group received ketofol in combination with midazolam. In a study by Blunch et al., the effect of midazolam was examined on amnesia induction and it was shown midazolam in a dose-dependent manner can create anterograde amnesia in adults. The two studies are similar in terms of methodology (11).Silva Lucas in 2011 examined children undergoing bone marrow aspiration and reported that the combination of propofol and ketamine with a 1: 1 concentration can accounts for sedation, appropriate analgesia, and quick recovery without excreting adverse complications that is in line with the current study with respect to benefits and safety of ketamine in combination with propofol (9); however, they did not investigate amnesia in children (12).Hsiao PC et al., evaluated and compare the impact of postoperative sedation after major surgery with midazolam or propofol on amnesia and anxiety in conscious patients under intensive care. In line with this study, they concluded that both midazolam and propofol are effective amnesic and anxiolytic drugs and midazolam can have more favorable effects on amnesia and they recommended a combination of these two drugs simultaneously in ICU patients (13).In a study by Kucukyavuz Z, et al., in 2004, the effects of low-dose midazolam with propofol for patient control sedation (PCS) in 30 healthy (ASA grade I) patients who were randomly allocated into two equal groups (n=15 in each) were studied. They concluded that low-dose midazolam with propofol neither reduced oxygen saturation nor prolonged the time of discharge during PCS. Moreover, they reported that low-dose midazolam with propofol can also increase the acceptability and comfort for patients and made the operation easier, which makes it preferable to propofol alone (14). Their findings were also

consistent with h the present study.A prospective, double-blinded, randomized trial was conducted on emergency department (ED) patients requiring procedural sedation and analgesia (PSA) for repair of deep traumatic lacerations and reduction of bone fractures, to compare the ketamine/propofol (ketofol) combination with the midazolam/fentanyl (MF) combination by Nejati et al., (2011) (15). According to their study, the ketamine/propofol combination brings about adequate sedation and analgesia for painful procedures and seems to be a safe and useful technique in the ED. Akin et al., explored the effects of propofol and propofol-ketamine in a prospective, randomized, double-blind study on hemodynamics, sedation level, and recovery period in pediatric patients undergoing cardiac catheterization. They also concluded that propofol combined with low-dose ketamine preserves mean arterial pressure better without impacting the recovery and thus is a good option in pediatric patients undergoing cardiac catheterization (16). Mittal et al., in a double blind randomized trial compared ketofol versus propofol for endodontic treatment of anxious pediatric patients. They presented that both the regimen exhibited similar sedation profile while propofol alone can be safer option (17).

Conclusion

According to the results of the present study and in line with previous studies, it can be concluded that low-dose ketamine in combination with propofol in a way that the dose of propofol was higher than ketamine may results in fewer side effects in children.

Conflict of interest

The authors declare that there is no conflict of interest.

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