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Safety of Deep Sedation with General Anesthesia for Minor Invasive Procedures in Pediatric Hematology/Oncology Patients

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Abstract

Background: Multiple invasive procedures are routinely performed in diagnosis and treatment of hematologic/oncologic diseases. Because these procedures are painful, they may cause stress and anxiety in patients and their parents. Especially in patients with malignancies, the repeating procedures can lead to psychiatric disorders like depression and post-traumatic stress disorders. Therefore, general anesthesia is recommended during these invasive procedures for pain control.
Objectives: The goal of this study was to evaluate safety and outcome of deep sedation with general anesthesia in hematology/oncology patients during invasive interventions in pediatric outpatient sedation unit.
Methods: We retrospectively analyzed records of 129 patients (59 girls and 70 boys) who had undergone 155 invasive procedures with general anesthesia. Patient demographics, reason of operations, anesthesia complications, duration of procedures, and time for recovery from anesthesia were recorded from anesthesia charts. Patients received ketamine (maximum dosage 2 mg/kg) plus midazolam, ketamine plus midazolam plus sevoflurane inhaler (sevoflurane inhaler was added when 2 mg/kg of ketamine was inadequate to obtain deep sedation) and sevoflurane inhaler in 140, 10 and 5 of operations, respectively.
Results: Complications occurred in 31 (20%) of these operations. Majority of complications were mild and included post-op agitation, vomiting and local pain which occurred in 6, 5 and 4 of the operations, respectively. Only 2 patients developed severe complications (fall off the stretcher and bronchospasm) which did not lead to any long term morbidity. The complication rate did not differ according to the anesthetic drugs, reason of operations or patient demographics.
Conclusions: In this group of patients, deep sedation with general anesthesia in an outpatient sedation unit, administered by trained professionals, was safe, quick, and effective for short-term invasive painful procedures.

Keywords: General Anesthesia, Midazolam, Ketamine, Pain Management

1. Background

The diagnose of many blood disorders and treatment of several malignancies in childhood necessitate short-term painful procedures like lumbar puncture (LP), intrathecal chemotherapy (IT QT), bone marrow aspiration (BMA) and bone marrow biopsy (BMB). Adults may tolerate these painful procedures with infiltration of local anesthetics at the operation site but children need help to reduce their pain because they are not accustomed to pain (1).

Management of these painful procedures varies among institutions. Benzodiazepines are unfortunately commonly used in pediatric out-patient clinics during invasive procedures for amnestic and hypnotic effects, even though they lack analgesic properties (2). This contributes to the anxiety of patient and makes the procedure difficult for patient and medical staff (3). The negative impact of these painful interventions in patients are worse particularly when they have to be repeated many times during treatment (4, 5). Existing of pain during operation causes lots of stress in the parents as well. The American Academy of Pediatrics and World Health Organization recommend applying general anesthesia during painful interventions in pediatrics (6, 7). On the other hand, due to restricted inpatient capacity and increased inpatient clinic expenses, diagnostic procedures in outpatient clinics are becoming more and more frequent.

In the last 18 months in our Pediatric Hematology and Oncology Clinic, which is a reference center for Middle East of Turkey, general anesthesia has been used routinely to obtain deep sedation during invasive painful procedures like BMA, BMB, LP and IT QT in an outpatient sedation unit. In this study we will report all the complications during and

after these procedures related to general anesthesia in this population.

2. Methods

This retrospective study was conducted in order to evaluate side effects of deep sedation with general anesthesia in patients in Pediatric Hematology and Oncology Clinic between January 2014 and August 2015 in a period eighteen months. The procedures were performed electively under general anesthesia in a sedation unit at outpatient clinic where resuscitation equipment, oxygen, suction and monitors were ready. All operations were carried out by an expert Hematologist. Procedural anesthesia and sedation was managed by an anesthesiologist. One hundred twenty nine children, who required 155 painful interventions for diagnosis or treatment of hematologic and oncologic diseases, were enrolled in this study. All children had fasted 4 - 6 hours before the procedure. Inclusion criteria were defined as: All patients with hematologic and oncologic disorders between one month to 18 years of age who have undergone painful operations like BMA, BMB, LP and IT QT with deep sedation; Ramsay sedation score (RSS) $\geq$ V (8). Exclusion criteria were mild or moderate sedation according to Ramsay sedation scale, having any cardiopulmonary disease, patients below one month of age or over 18 years old and American Society of Anesthesiology (ASA) class $\geq$ 3 (9).

We retrospectively collected data about reason of operation (diagnostic or therapeutic), gender, age and weight of patient, type of procedure, species of anesthetic drugs, type of venous access, time for recovery from anesthesia (the time beginning from the last dose of sedation up to the moment when the patients opened their eyes or gave an age-appropriate verbal response) and type of complications from the files and anesthesia charts of patients. Complications occurred from beginning of anesthesia to completion of procedure and transfer to the recovery room were defined as intraoperative while the ones which were seen in recovery room were classified as postoperative complications. Anesthesia complications recorded included abnormal heart beat (< 20% of baseline was defined as bradycardia and $\geq$ 20% of baseline was defined as tachycardia), abnormal blood pressure (hypertension is defined was > 90th percentile of and hypotension was defined as < 5th percentile of normal blood pressure), desaturation (defined as decrease in arterial oxygen concentration < 93%), laryngospasm, bronchospasm, vomiting, hypothermia (< 35°C), hyperthermia (> 37.8°C), traumatic LP, agitation, local pain and signs of allergy.

2.1. Statistical Analysis

Statistical analysis was made using IBM SPSS statistics, for Windows, version 22.0 (IBM Corp., Amonk, NY). Fisher's exact test and Pearson Chi-square analysis were performed for categorical variables. The normality assumptions were controlled by the Shapiro-Wilk test. The differences between two groups were evaluated with Mann-Whitney U test for non-normally distributed data. Results are expressed as No. (%), mean $\pm$ standard deviation (SD) or median (min - max). P values < 0.05 were considered statistically significant.

3. Results

Between January 2014 and August 2015, 166 procedures were performed over 136 patients with general anesthesia. Among these operations 11 were excluded because they had been conducted with ASA $\geq$ 3 (9). Eventually 155 procedures over 129 patients with a median of 1.2 operations per patient were included in the study.

Of the 129 individuals 70 (54%) were boys and 59 (46%) were girls. The mean age of patients was 61 months (range: 1 month to 15 years). The median weight was 16 kg, ranging from 3 to 70 kg. Reasons of operations were diagnosis of disease, treatment of malignancies (intrathecal chemotherapy), staging of tumor and evaluation of treatment response in 111, 25, 15 and 4 of the operations respectively (Table 1).

Among the 155 procedures, 38 were conducted in patients with solid tumors, 18 in patients with hematologic malignancies and the rest 99 in patients with benign hematologic diseases. In 11 of the operations central line of patient (Port-a-Cath) was used for delivering IV drugs while the rest 144 received IV drugs via peripheral line.

The most frequent procedure was BMA (n: 79, 51%); followed by BMB and BMA (n: 44, 28.4%), IT QT (n: 28, 18.1%), BMA and LP (n: 2, 1.3%) and LP (n: 2, 1.3%). Procedures lasted for a median of 2 minutes, ranging from 1 minute to 15 minutes; generally shortest were BMA followed by LP, IT QT, BMB and BMA and BMA and LP in the last place (Table 1).

Deep sedation with general anesthesia was provided with IV ketamine plus IV midazolam, IV ketamine plus IV midazolam plus sevoflurane inhaler (in oxygen 3.3%) and sevoflurane inhaler in 140, 10 and 5 operations, respectively. Mean ketamine dose was 1.2 mg/kg ranging from 1 to 2 mg/kg for inducing anesthesia. Midazolam was applied in combination of ketamine with a dose of 0.5 mg (for children less than 10 kg) or 1 mg (for children exceeding 10 kg) to provide more rapid onset of analgesia. All children had optimal deep sedation for procedure with a RSS $\geq$ V.

Table 1. Demographic Data of Patients, Type and Reason of Operations (N = 155)[a]

Variables	Value
Age, mo	
Mean ± SD	61 ± 45.6
Median (min - max)	60 (1 - 180)
Gender	
Male	70 (54.3)
Female	59 (45.7)
Weight, kg	
Mean ± SD	18.1 ± 11.6
Median (min - max)	16 (3 - 70)
Reason of operation	
Diagnostic	111 (71.6)
Treatment (hematologic/oncologic malignancies)	25 (16.1)
Staging	15 (9.7)
Evaluation (tumor)	4 (2.6)
Procedure	
BMA	79 (51)
BMB + BMA	44 (28.4)
IT QT	28 (18.1)
BMA + LP	2 (1.3)
LP	2 (1.3)
Duration of operation, min	
Mean ± SD	3 ± 2.3
Median (min - max)	2 (1 - 15)
Type of venous access	
Peripheral vein	144 (92.9)
Central venous access	11 (7.2)
Type of anesthetic drugs	
Ketamine + midazolam	140 (90.3)
Ketamine + midazolam + sevoflurane	10 (6.5)
Sevoflurane	5 (3.2)
Dose of ketamine, mg/kg	
Mean ± SD	1.2 ± 0.3
Median (min - max)	1 (1 - 2)
Duration of recovery from anesthesia	
Mean ± SD	11.3 ± 2.8
Median (min - max)	10 (8 - 30)
Complication	
No	124 (80)
Yes	31 (20)

Abbreviations: BMA, bone marrow aspiration; BMB, bone marrow biopsy; IT QT, intrathecal chemotherapy; LP, lomber puncture.
[a]Values are expressed No. (%) unless otherwise indicated.

Table 2. Details of Complications[a]

Complications	Intraoperative	Postoperative
Agitation	-	6 (19.35)
Vomiting	-	5 (16.13)
Local Pain	1 (3.23)	3 (9.68)
Headache	1 (3.23)	2 (6.45)
Laryngospasm	2 (6.45)	-
Tachycardia	2 (6.45)	-
Hypertension	2 (6.45)	-
Hypothermia	2 (6.45)	-
Local bleeding	2 (6.45)	-
Desaturation	1 (3.23)	-
Bronchospasm	1 (3.23)	-
Fall off the stretcher	1 (3.23)	-
Total	15 (48.39)	16 (51.61)

[a]Values are expressed as No. (%)

Median time of recovery from anesthesia was 10 minutes ranging from 8 to 30 minutes (Table 1).

None of the 155 patients on operation required intubation or cardiorespiratory rescue or transfer to intensive care unit. All of the operations were successfully completed; none of them had to be suspended for any reason. There were no complications resulting in long-term morbidity or mortality in our median 16 months of follow up (range: 4 - 23 months).

Complications occurred in 31 of 155 (20%) operations. Details of complications are shown in Table 2. There were no statistically significant differences in terms of patient demographics, type of operation, recovery from anesthesia, reason of operation, characteristics of anesthetics and dosage of ketamine between those patients who experienced adverse events and those who did not (Table 3).

The most common adverse event was short term mild recovery agitation (n: 6) followed by vomiting (n: 5) which were both observed in post-op period and resolved spontaneously.

Laryngospasm (n: 2) and desaturation (n: 1) episodes which occurred intraoperatively were mild and reverted using oxygen, maneuvers to open airway and aspirating nasal-oral secretions. One patient had a moderate bronchospasm just after accomplishing BMA; he required transient bag valve ventilation for 5 minutes. He was kept in hospital for observation but no complication occurred later.

Pain at operation site (n: 4) and headache (n: 3) were treated successfully with oral pain killers. Intraoperative

Table 3. Comparasion of Demographic and Clinical Characteristics of Patients Between Groups[a]

	Complication		
	No (N = 124)	Yes (N = 31)	P Value
Gender			0.846[b]
Male	56 (53.8)	14 (56)	
Female	48 (46.2)	11 (44)	
Weight	16 (3-70)	17 (3-60)	0.087[c]
Reason of operation			NA
Diagnostic	88 (71)	23 (74.2)	
Treatment (hematologic/oncologic malignancies)	21 (16.9)	4 (12.9)	
Staging (tumor)	12 (9.7)	3 (9.7)	
Evaluation (tumor)	3 (2.4)	1 (3.2)	
Procedure			NA
BMA	63 (50.8)	16 (51.6)	
BMB + BMA	35 (28.2)	9 (29)	
IT QT	24 (19.4)	4 (12.9)	
BMA + LP	1 (0.8)	1 (3.2)	
LP	1 (0.8)	1 (3.2)	
Duration of operation, min	2 (1-15)	2 (1-7)	0.760[c]
Venous access			0.461[d]
Peripheral vein	116 (93.5)	28 (90.3)	
Central venous access	8 (6.5)	3 (9.7)	
Type of anesthetic drugs			NA
Ketamine + midazolam	113 (91.1)	27 (87.1)	
Ketamine + midazolam + sevoflurane	7 (5.6)	3 (9.7)	
Sevoflurane	4 (3.2)	1 (3.2)	
Dose of ketamine, mg/kg	1 (1 - 2)	1 (1 - 2)	0.593[c]
Duration of recovery from anesthesia	11 (8 - 30)	10 (8 - 14)	0.705[c]

Abbreviation: BMA, bone marrow aspiration; BMB, bone marrow biopsy; IT QT, intrathecal chemotherapy; LP, lomber puncture; NA, not applied.
[a] Values are expressed as No. (%) and median (min - max).
[b] Pearson chi-square test.
[c] Mann-Whitney U test.
[d] Fisher's exact test.

hypertension (n: 2) and tachycardia (n: 2) was transient and spontaneously resolved. Intraoperative hypothermia (n: 2) was treated with warming blankets and local bleeding after LP was treated with extra bandage (n: 2). One thrombocytopenic patient fell off the stretcher and bit his tongue while he was recovering from anesthesia. He was treated with thrombocytes suspension. Computed tomography imaging was free of hematoma or intracranial bleeding. He was kept in hospital for 24 hours for observation but he did not suffer from any complication related to this trauma.

4. Discussion

Different strategies have been used to reduce pain during invasive interventions in children with hematologic and oncologic disorders. While conscious sedation is enough for minimally invasive procedures, deep sedation is needed for more invasive interventions (8). But physicians usually face a main obstacle while considering general anesthesia for these interventions; parents fear about safety of general anesthesia. This is why we report the incidence of complications resulting from exposure to anesthetic drugs in our study. Is it acceptable and is there any factor influencing this rate?

In our institution, ketamine in combination with midazolam was chosen to induce anesthesia in majority of operations according to some literatures that have shown that this combination has a low rate of complication and a shorter recovery time (10, 11). In 140 of operations this combination was enough to obtain deep sedation. Because several studies have demonstrated increased complication rate with high dose of ketamine, instead of applying more ketamine, sevoflurane inhaler (in oxygen 3.3%) was added to maintain anesthesia in 10 of the operations where 2 mg/kg ketamine was not enough to sustain deep sedation (12, 13). Complications occurred in 27 of 140 operations where ketamine and midazolam was used and in 3 of 10 interventions where sevoflurane was added to reach an adequate level of sedation.

In a report from Traivaree et al. side effects were noted in all children who were operated for hematologic malignancies with ketamine sedation. Nausea and vomiting were reported at half of the operations (14). Complications were noted in 16 of 43 (37%) operations with a fixed dose of ketamine in adolescent patients in a pediatric emergency department for procedural sedation (15). Nausea (n: 7) and vomiting (n: 5) were again the most frequent reported complications. In our study, 5 of the 150 (3.3%) operations with ketamine were complicated with nausea and vomiting. We have observed less gastrointestinal problems compared to literature, this might be due to low dose of ketamine (max: 2 mg/kg) usage in our patients.

Recovery agitation is a well-known side effect of ketamine anesthesia. In the literature the frequency differs from 0.4% - 50% (16, 17). In the meta-analysis of clinical trials with ketamine sedation, recovery agitation was reported as 10% among 8380 operations (18). We have observed agitation in 6 (3.9%) of our operations. Agitations dissolved spontaneously, none of them required pharmacological intervention, so they were clinically unimportant. The low frequency of agitation in our study may be a result of concurrent use of midazolam with ketamine. Tsai et al have demonstrated that combination of ketamine, midazolam and sevoflurane decreased incidence of sevoflurane induced agitation (19). We have seen no recovery agitation in our patients who were operated with this combination, but, because of the small number of patients (n: 10), our study was not powered to support this hypothesis.

Extreme salivation is a known side effect of ketamine. In the largest meta-analysis of 8282 pediatric patients with ketamine anesthesia, the overall incidence of airway and respiratory adverse events was reported to be 3.9% (12). High intravenous dosing ($\geq$ 2.5 mg/kg initial dose or total dose $\geq$ 5.0 mg/kg), specific age (< 2 years and > 13 years), co-administration of anticholinergics or benzodiazepine were the factors associated with increased risk (12). In our study we have seen 3 (1.9%) respiratory side effects (laryngospasm; n: 2, bronchospasm; n: 1) with ketamine anesthesia. This low ratio may be related to low ketamine doses.

Ketamine has an indirect sympathomimetic effect. It causes stimulation of cardiac and central nervous system by blocking catecholamine reuptake (20). In therapeutic doses, ketamine can exert a mild sympathomimetic effect on the cardiovascular system with slight increases in blood pressure and heart rate (21). The prevalence of hypertension and tachycardia was reported 0% - 2.3% in the literature (10, 22, 23). In our study 2 patients developed tachycardia and 2 patients developed hypertension. Our ratio of 2.7% is in accordance with the literature.

Due to potent effect, quick induction, rapid and predictable recovery from anesthesia, sevoflurane inhaler (in oxygen 3.3%) was picked for inducing anesthesia in infants (n: 5) less than 3 months of age in our study. Desaturation was seen in one of these 5 patients (20%). Airway obstructions (8%), laryngospasm (2% to 8%), breath-holding (2% - 5%), apnea (2%) are the reported respiratory side effects of sevoflurane (24). Sevoflurane depresses the circulation in a dose-dependent manner that is easily reversible by decreasing the anesthetic concentration, and/or administering atropine (25). In our study, desaturation was transient and did not need any treatment. Previously reported side effects like post anesthesia agitation or epileptiform ECG activity was not detected in our study (26, 27) probably because our sample size is was too small to detect adverse events with low incidence.

Except in the 2 patients (1 patient with moderate bronchospasm and 1 patient who fell off the stretcher), rest of the observed complications were mild; most of these side effects could even be considered as physiological reactions to medications and that would unlikely be reported in other studies. This shows safety of the anesthetics we applied. For this reason, we recommend to apply ketamine in low doses (max: 2 mg/kg) combined with midazolam and administration of sevoflurane when this combination was not enough to maintain anesthesia instead of higher ketamine doses.

4.1. Conclusion

On the basis of the data from this study we conclude that, general anesthesia with deep sedation administered by a special team in outpatient clinic, provides adequate and safe sedation for minor invasive procedures in our patients. We recommend to use ketamine in low doses (max: 2 mg/kg) which was quite safe in our patients. Due to

low number of patients in sevoflurane containing anesthesia regimens, we cannot compare side effect profile of the anesthesia protocols we used. Further, prospective studies are needed to replicate our findings and to assess the impact of sevoflurane combined regimens.

Footnotes

Authors' Contribution: Gulen Tuysuz designed and wrote the article and analyzed the data, Funda Tayfun revised the manuscript for intellectual content and made the statistical analysis.

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