Effects of Different Anesthetic Agents on Surgical Site Hemorrhage During Circumcision

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Purpose: To investigate the effects of ketamine+midazolam and propofol+sevoflurane anesthesia on surgical site hemorrhage during circumcision procedures.

Materials and Methods: The boys undergoing circumcision surgery were included in the study. The patients were divided into two groups. In Group 1 (n = 50), 0.01 mg/kg midazolam and 2 mg/kg IV ketamine were administered. In Group 2 (n = 50), 1 µg/kg fentanyl, 1 mg/kg lidocaine 2%, and 2–3 mg/kg IV propofol were administered, and patency of airway was ensured with a laryngeal mask airway. The intraoperative bleeding scale was recorded during the procedure to evaluate surgical site bleeding. Hemorrhage was checked for the first three hours using the postoperative bleeding scale to follow the amount of hemorrhage.

Results: Intraoperative bleeding scores were significantly higher in Group 1 as compared to Group 2. However, there was no significant difference between the groups regarding frequency of postoperative hemorrhage. The mean blood pressure values measured at 5th, 10th, 15th minutes and recovery room were significantly higher in Group 1.

Conclusion: The intraoperative bleeding scores were significantly higher with ketamine+midazolam compared to propofol+sevoflurane. On the other hand this hemorrhage can be controlled easily with appropriate hemostasis, and the amount of blood loss was not clinically significant. We think that our study makes a positive contribution to the literature about the effects of anesthetics on the surgical site bleeding during circumcision.
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Keywords: circumcision; hemorrhage; ketamine; midazolam; propofol.

INTRODUCTION

Circumcision, is one of the most widely performed surgical procedures worldwide. Circumcision is performed at varying rates in various populations and age groups. [1,2] Currently, approximately one quarter of men in the world are circumcised largely concentrated in the USA, Canada, countries in the middle east and Asia with Muslim population and large portions of Africans.[3,4] In a study conducted in USA, estimated circumcision prevalence was 80.5% and prevalence varied significantly by year of birth, race/ethnicity, health insurance type, and family income.[5] It is most commonly performed for religious reasons and it may also be performed for medical reasons, including prevention of phimosis, paraphimosis, urinary tract infections, and various other types of infections (i.e. Balanitis xerotica obliterans).[2,6] The most common early complications of circumcision include pain, hemorrhage, swelling, and inadequate skin removal. Hemorrhage is the most common complication, with a 0.1–35% incidence rate. This type of hemorrhage is very mild and can be controlled by applying direct pressure to the site for a few minutes.[6]

It has been reported that circumcision can be performed without anesthesia in the neonatal period or with local anesthesia in older individuals as day surgery. The widely accepted opinion suggests the use of general anesthesia or sedation, considering the psychological impact of this painful and stressful procedure on a child. The ideal anesthesia should ensure appropriate analgesia, amnesia, sedation, inactivity, and early recovery from anesthesia without cardiovascular or respiratory depression, nausea/vomiting, or agitation.[8] Several anesthetic agents and their combinations have been used for those purposes. One of the most commonly preferred agents is propofol, which acts by facilitating GABA inhibitory neurotransmission. However, propofol may cause cardiovascular and respiratory depression. Ketamine acts via direct sympathetic stimulation and reuptake inhibition of norepinephrine from the postganglionic sympathetic system. This agent also induces functional dissociation between the limbic and cortical systems, called "dissociative anesthesia". Due to its high therapeutic index and ability to maintain airway protective reflexes during sedation, ketamine is considered appropriate for sedoanalgesia.[8]

In our literature review, we did not find any studies

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Table 1. Intraoperative and postoperative bleeding scale.

	Intraoperative	Postoperative
0	No hemorrhage	No hemorrhage
1	Slight hemorrhage; no compression via gauze of blood required	Slight hemorrhage: small amount of staining at the incision line
2	Slight hemorrhage; occasional compression via gauze required. Surgical field not threatened	Moderate hemorrhage: bleeding stains the dressing
3	Slight hemorrhage; frequent compression via gauze required. Hemorrhage threatened surgical field but a few seconds after compression via gauze bleeding was removed	Severe hemorrhage: bleeding continues despite of dressing
4	Moderate hemorrhage; frequent compression via gauze required. Hemorrhage threatened surgical field directly after gauze compression was removed	

about the effects of anesthetics on surgical site hemorrhage during circumcision. As such, in this study, we aimed to compare the effects of ketamine+midazolam and propofol+sevoflurane anesthesia on surgical site hemorrhage during circumcision procedures.

MATERIALS AND METHODS

Study design
This study was a prospective single center study. It was conducted in accordance with the principles of the Declaration of Helsinki. The patients' families were interviewed in the anesthesia outpatient clinic during the preoperative period to obtain approval for their children's participation in the study. A written informed consent was obtained from each patient' families. The study protocol was approved by the Local Ethics Committee and Australian New Zealand Clinical Trials Registry (Ref: ACTRN12616000189426).

Study population
Study participants were boys undergoing circumcision surgery in Bursa Yuksek Ihtisas Training and Research Hospital from October 2014 to January 2015. Patients were enrolled in the study after a routine preoperative evaluation. Inclusion criteria were boys undergoing circumcision surgery. Patients who showed contraindications for general anesthesia (malignant hyperthermia history, toughness, etc.); instead of a history of allergy to anesthetic drugs or known bleeding diathesis; instead of abnormalities in coagulation tests; instead of American Society of Anesthesiologists (ASA) physical status was III–IV; or whose circumcision was performed with another surgeon were excluded from the study. Patients' enrollment algorithm has been illustrated in **Figure 1**.
Procedures
Following 4–6 hours of fasting and premedication with 0.01–0.02 mg/kg IV midazolam (Zolamid®, Defarma, Ankara, Turkey), the patients were taken to the operating room. Mean blood pressure (MBP), heart rate (HR), and peripheric oxygen saturation were monitored and recorded for all patients in the preoperative and intraoperative periods, as well as in the recovery room.
In Group 1 (n = 50), 0.01 mg/kg midazolam and 2 mg/kg IV ketamine (Ketalar®, Pfizer, Istanbul, Turkey) were administered by an anesthesiologist, and the pa-

tients were given 2–3 L/minute O2 through an oxygen mask. A sedation score of 3 was determined according to the Ramsay Sedation Scale. When an additional dose was needed during the operation, 0.5 mg/kg ketamine was administered.
In Group 2 (n = 50), 1 µg/kg fentanyl (Talinat®, Vem, Istanbul, Turkey), 1 mg/kg lidocaine 2% (Jetmonal®, Adeka, Istanbul, Turkey), and 2–3 mg/kg IV propofol (Propofol 2%®, Fresenius Kabi, Bad Hamborg, Germany) were administered. The patency of airway was ensured with a laryngeal mask airway (LMA). Anesthesia was maintained using 2–3% sevoflurane (Sevorane®-Likit 100%, AbbVie, Queenborough Kent, England), 1 L/minute O_2 and 1 L/minute nitrous oxide (N_2O).

Surgical technique
All circumcisions were performed by one surgeon, who was unaware of the groups in this study. After appropriate surgical site cleaning, a dorsal penile nerve block was performed with 2 ml 0.5% bupivacaine (Bustesin®, Vem, Ankara, Turkey) in both groups. The skin and mucosa were then separated, a circumferential incision was made on the outer prepuce at the level of the corona, and hemostasis was ensured with bipolar cautery. The wound edges were sutured with 5/0 polyglactin 910 (Vicryl Rapide™, Ethicon). The procedure was completed with loose dressing. Additional drug requirements and duration of the operations were recorded. The intraoperative bleeding scale defined by Kumari et al. was used (**Table 1**).[9]

Evaluations
Length of recovery room stay was recorded for each patient, and a Faces Pain Scale (FPS) was used for pain assessment (0:no hurt, 1:hurts little bit, 2:hurts little more, 3:hurts even more, 4:hurts whole lot, 5:hurts worst). When the Modified Aldrete's Score (MAS) was 9–10, the patients were transferred to the ward.[10] Hemorrhage and pain were followed up in the ward. Hemorrhage was checked for the first three hours using the postoperative bleeding scale (**Table 1**). When FPS was ≥ 2, 10 mg/kg paracetamol suppository (Paranox S®, Sanofi Aventis) was administered. Total postoperative analgesic requirements and intraoperative and postoperative complications were recorded.

Table 2. Demographic characteristics of groups.

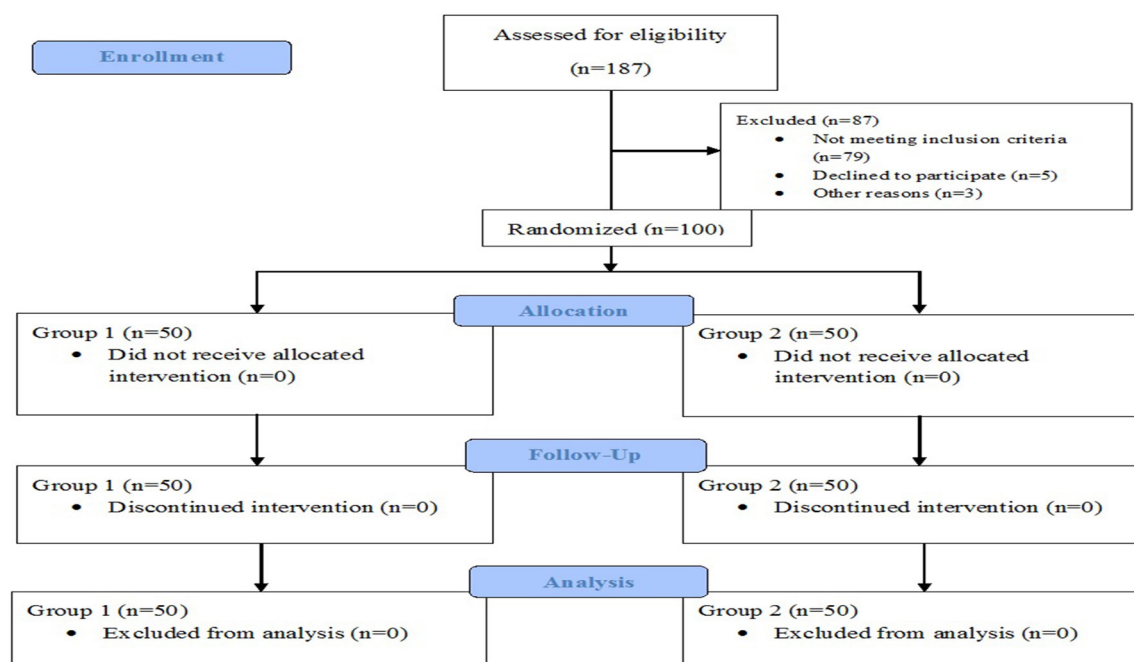| Variables	Group 1 (N = 50)	Group 2 (N = 50)	P-value
Age, year; mean ± SD (range)	5.82 ± 2.23 (1-8)	5.48 ± 2.24 (1-8)	.448
Weight, kg; mean ± SD (range)	20.09 ± 5.27 (9-31)	21.14 ± 7.32 (8-36)	.413
ASA* I / II; n	46 /4	47 / 3	
Operation time, minute; mean ± SD (range)	14.12 ± 3.7 (10-25)	15.3 ± 3 (10-20)	.087

*ASA: American Society of Anesthesiologists

Figure 1. Trial Flow Diagram.

Outcomes

Primer outcomes: The score of intraoperative bleeding scale, and postoperative bleeding scale were evaluated. Seconder outcomes: MBP, HR, and peripheric oxygen saturation were evaluated in the preoperative - intraoperative periods, and in the recovery room. FPS, total postoperative analgesic requirements, intraoperative and postoperative complications were also assessed.

Statistical analysis

Statistical Package 21.0 for Windows (SPSS Inc., Armonk, NY, USA) was used for statistical analyses. The Shapiro-Wilk test was used to analyze normal distribution of the data. *T*-test was used to compare two groups with normally distributed data and quantitative variables. The Wilcoxon sign-rank test was used to compare the dependent samples. In the analysis of repeated measures, percentage changes from baseline were calculated and compared using these values. The Pearson's chi-square, and Fisher's exact chi-square were used to analyze categorical data. Mean ± standard deviation, frequency, and percentage were used for definitive statistics of the data. If the *P* value was < .05, the results were considered statistically significant. Based on our pilot data, sample size was calculated with a power of 0.8 and a risk of for type 1 error to detect 0.5 effect size of intraoperative bleeding score for both groups. At least 50 patients per group were required.

RESULTS

Of 187 patients assessed for eligibility, 79 patients did not meet the inclusion criteria, five patients declined to participate in the study, and three patients (early discharge from hospital) were excluded for other reasons. Of the 100 patients included, 50 were allocated to Group 1 and 50 to Group 2. None of the patients dropped out during the study (**Figure 1**). There were no significant differences between the two groups with respect to age, weight, ASA class, or duration of operation (*P* > .05, **Table 2**).

Primary outcomes:

Intraoperative bleeding scores were significantly different between the groups (**Figure 2**, *P* = .001). Although hemorrhage was controlled with appropriate hemostasis, the prevalence of hemorrhage that could fill the surgical site was significantly higher in Group 1 compared to Group 2. However, there was no significant difference between the groups regarding postoperative bleeding scores (Group 1: 0.14 ± 0.4, Group 2: 0.04 ± 0.19, *P* = .120).
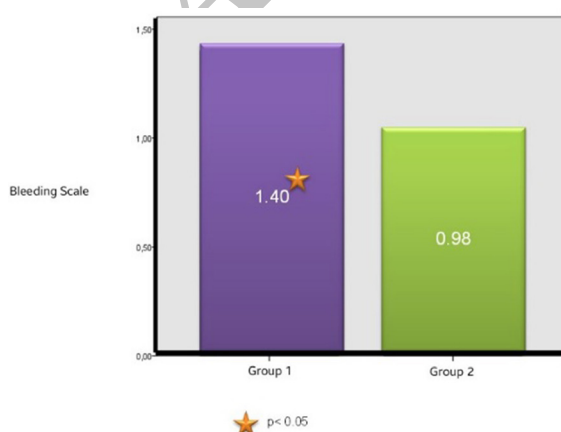
Secondary outcomes:
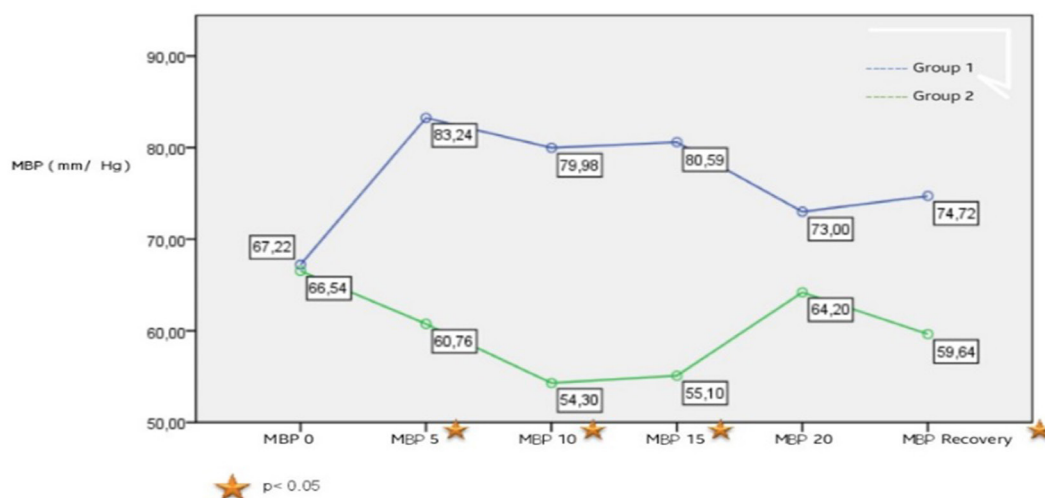

Figure 2. Bleeding Scale of the Groups.

Figure 3. Values of Mean Blood Pressure (MBP).

The MBP values measured at 5th, 10th, 15th minutes and recovery room were significantly higher in Group 1 ($P < .05$, **Figure 3**). The HR values measured at 15th, and 20th minutes were significantly higher in Group 1 ($P < .05$, **Figure 4**). No statistically significant differences in SpO2 levels during surgery or in the recovery room were found between Groups 1 and 2 ($P > .05$). The additional ketamine dose requirement during circumcision was 58% in Group 1.

There was no significant difference in length of recovery room stay between the two groups (Group 1: 14 ± 2.3 minutes and Group 2: 15 ± 1.8 minutes, $P > .05$). When MAS was considered, there was no difference in time to reach a 9–10 MAS score between the groups (Group 1: 13.2 ± 3.3 minutes, Group 2: 14.4 ± 1.6 minutes, $P > .05$). There was no statistically significant difference between the groups in FPS measured in the recovery room (Group 1: 1.23 ± 0.32, Group 2: 1.284 ± 0.30, $P > .05$). Similarly, no significant difference was detected statistically between the groups in FPS measured during the stay in the ward (Group 1: 1.14 ± 0.35, Group 2: 1.14 ± 0.35, $P > .05$). Six patients in Group 1 and seven patients in Group 2 had FPS scores ≥ 2. A 10 mg/kg paracetamol suppository was administered in

the postoperative period to those patients. Postoperative analgesic requirement was $\leq 18\%$ in both groups.

No severe anesthesia-related or surgery-related complication developed in any of the patients during or after the operation. In Group 1, we observed the following complications: decrease of SpO_2 levels below 95% in 2% of patients, excessive secretion in 6% of patients, vomiting in 4% of patients, laryngospasm and cough in 2% of patients, and allergy in 2% of patients. In Group 2, we observed the following complications; decrease of SpO_2 levels below 95% in 2% of patients, laryngospasm in 8% of patients, cough in 4% of patients, and allergy in 6% of patients and waking up late in 6% of patients. The incidence of complications was higher in Group 2, but this difference between groups was not statistically significant.

DISCUSSION

We investigated the effects of ketamine+midazolam and propofol+sevoflurane anesthesia on surgical site hemorrhage during circumcision procedures. Our main finding from our study was that the intraoperative bleeding scores were higher in the ketamine+mida-
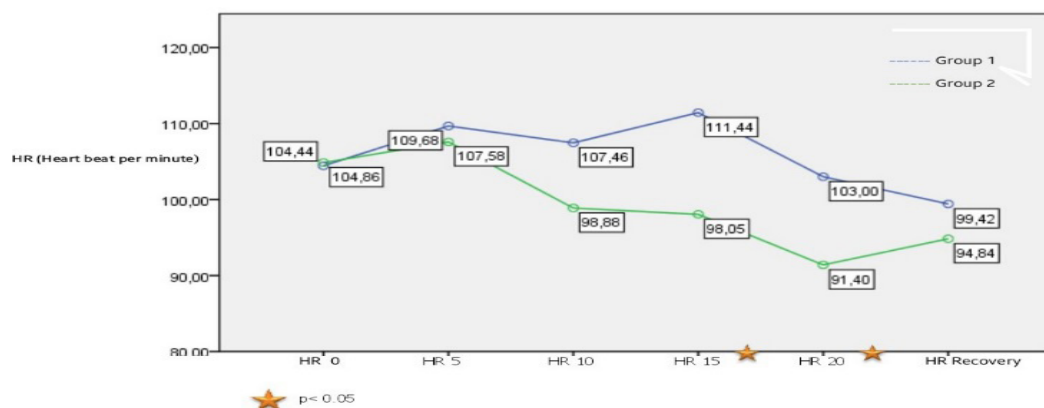

Figure 4. Value of Heart Rate (HR).

zolam group compared to propofol+sevoflurane group, but postoperative bleeding scores were not significantly difference between the groups. There was no difference in the length of recovery room stay between two groups. While circumcision is mostly performed as a religious ritual, it may be also performed to reduce risks of urinary tract infections, penile malignancy, and sexually transmitted illnesses. Besides, circumcision does carry a risk of complications. There are several factors involved in the development of complications, such as anatomical abnormalities, additional diseases, surgical technique, and patient's age[11] It has been reported that even in experienced hands, the rate of complications associated with circumcisions is 2–10%. While hemorrhage is the most common complication of circumcision, other problems include insufficient or excessive foreskin removal, adhesions, injury to the urethra, necrotizing fasciitis, and amputation.[12] Hemorrhage is mostly related to overlooked control of hemostasis during the procedure.[11]

The current study was planned as a result of observations of this procedure suggesting that hemorrhage tendency might vary depending on the method of anesthesia. In the present study, we preferred to use the intraoperative bleeding scale that Kumari et al. used for day case surgeries.[9] We did not need to follow hemoglobin level, test of bleeding time to detect intraoperative and postoperative hemorrhage as we do not expect major hemorrhage during circumcisions.

In our study, the intraoperative bleeding scores were significantly higher in Group 1 than in Group 2. In addition, the prevalence of hemorrhage that could fill the surgical site but could be controlled with appropriate hemostasis was significantly higher in Group 1. There was no significant difference in postoperative hemorrhage between the groups. Therefore, hemodynamic parameters were implicitly analyzed in order to identify the effects of the anesthetic agents administered to the patients. For ketamine, the peak effect starts in 2–3 minutes, the distribution half-life is 8–9 minutes, and the elimination half-life lasts for 2.2–2.9 hours.[13] This might be the reason for high blood pressure at 5 th, 10 th, and 15 th minutes, as well as the significant increase in intraoperative bleeding scores that we found in this study.

Direct and indirect effects of ketamine may lead to an increase in hemorrhage tendency. Depending on its dose, ketamine stimulates the sympathetic system directly and causes a secondary release of norepinephrine by depressing the baroreceptor reflex activity.[13-16] That may be the reason why intraoperative hemorrhage was significantly higher in Group 1. When ketamine was used in patients carrying a risk of hemorrhage, the patients were followed closely. Further studies are needed to reveal the effect of ketamine on the amount of hemorrhage. In addition, there was no significant difference in hemorrhage during the postoperative period between the groups, which might be due to the transient effects of ketamine. Blood pressure levels returned to normal during follow up in the ward. In our study, the blood pressure levels measured at 5, 10, and 15 minutes after operation in the intraoperative period and in recovery room were higher in Group 1 compared to Group 2. These differences may be due to the continuity of high blood levels of ketamine. In Group 2 the propofol+sevoflurane anesthesia lead to a hypotensive condition, which might account for the low hemorrhage tendency in the intraoperative period.

Perioperative and postoperative effects of ketamine have previously been reported. In a retrospective study, vomiting, decreased SpO_2 levels to 90%, agitation, and bronchospasm were reported as the complications of ketamine in day-case circumcision surgeries, at rates of 7.9%, 4.3%, 2%, and 1%, respectively.[17] In the present study, we administered 2 mg/kg ketamine and observed the following complications: decrease of SpO2 levels below 95% in 2% of patients, laryngospasm and cough in 2% of patients, vomiting in 4% of patients, increased secretion in 6% of patients, and allergy in 2% of patients. The incidence of complications was higher in Group 2, but this difference between groups was not significant.

An important limitation of the present study was the subjective bleeding scale. The amount of blood loss was not measured quantitatively such as comparison to preoperative and postoperative hemoglobin levels. Because the population of our study was children, we did not want to make invasive procedure. The other limitation was using a scale used in ear, nose, and throat surgery. No surgical bleeding scale used for circumcision was identified by our screening. In addition, a ketamine+propofol or ketamine+dexmedetomidine combination could have been used instead of ketamine+midazolam to minimize the increasing effect of ketamine on blood pressure.

CONCLUSIONS

Although propofol+sevoflurane is accompanied by less intraoperative blood loss compare to ketamine+midazolam during circumcision, this type of hemorrhage can be controlled easily with appropriate hemostasis and the amount of blood loss was not clinically significant. Ketamine + midazolam anesthesia have some superiority to propofol+sevoflurane as a continuation of spontaneous breathing, not using the other airway tools (LMA, endotracheal tube) and no prolongation in the length of recovery room stay. The results of this study demonstrate that ketamine + midazolam anesthesia can be a good alternative for circumcision. We think that our study makes a positive contribution to the literature about the effects of anesthetics on the surgical site bleeding during circumcision.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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