

A Comparative Study on The Effects of Tranexamic Acid and Controlled Hypotension with Remifentanyl on Blood Loss During Cleft Palate Repair

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Background: Tranexamic acid competitively inhibits the activation of plasminogen and is thus effective in reducing blood loss during surgery. This study aimed to compare the effects of tranexamic acid and hypotension with remifentanyl on blood loss during cleft palate repair.

Methods: This clinical trial study recruited 74 patients in Imam Hossein Hospital, Isfahan, Iran, during 2016-17. Children under three years of age who were candidates for cleft palate repair were randomly divided into two groups. The first group received an intravenous infusion of remifentanyl (0.1 µg/kg/min) after the induction of anesthesia. In the second group, an intravenous injection of 10 mg/kg tranexamic acid was slowly administered. The amount of blood loss and post-anesthesia care unit (PACU) stay duration were the main measured variables.

Results: The mean blood loss was 76.44 ± 14.7 and 57.76 ± 14.16 ml in the remifentanyl and tranexamic acid groups, respectively ($P < 0.001$). The mean duration of PACU stay was 64.59 ± 5.5 and 46.35 ± 4.4 minutes in the mentioned groups, respectively ($P < 0.001$).

Conclusion: There were no significant differences between the two groups in terms of demographic and baseline characteristics. According to our findings, tranexamic acid was more effective than remifentanyl in decreasing intraoperative blood loss and PACU stay.

Keywords: Tranexamic acid; remifentanyl; bleeding; cleft palate

Cleft palate is a common birth defect that can occur either alone or in combination with cleft lip. A cleft palate causes an opening into the nose and leads to breastfeeding and hearing problems, frequent ear infections, and impaired speech during childhood. The best time for the cleft palate repair is between nine and 18 months of age [1]. While the surgery takes a long time and is associated with a high risk of intraoperative bleeding, maintaining the hemodynamic stability of the patients is critical due to their very young age [1-2]. Various methods, including controlled hypotension using remifentanyl, have been recommended for maintaining hemodynamic stability and minimizing intraoperative bleeding during cleft palate repair [4-6]. Remifentanyl is a potent narcotic (twice as strong as fentanyl) with a short half-life which is metabolized by non-specific tissue and plasma esterases. It is administered at a dosage of 0.1-1.0 µg/kg/min together with a drug to maintain anesthesia [3].

Another method to decrease bleeding during cleft palate repair is the use of tranexamic acid which competitively inhibits plasminogen activation and thereby reduces the

conversion of plasminogen into plasmin (fibrinolysis) [7-8]. Since no study has so far compared the effectiveness of tranexamic acid and controlled hypotension with remifentanyl in reducing bleeding during cleft palate repair, this study aimed to compare these two methods.

Methods

This double-blind randomized controlled clinical trial was conducted at Imam Hossein Children's Hospital, Isfahan, Iran during 2016-17. In order to ensure a double-blind design, both the patients and the researcher were unaware of group allocations. The study population included cleft palate repair candidates aged below three years. Using a table of random numbers (prepared by a computer program), the participants were randomized to receive either remifentanyl or tranexamic acid.

Cleft palate repair candidates were included if they aged under three years, were ASA I class II, and had parental consent for participation. The patients were excluded if their surgery was cancelled for any reason or lasted for over three hours. A sample size of 35 subjects per group was determined by sample size estimation formula for comparison of two mean values and considering a confidence level of 95%, a test power of 80%, an estimated standard deviation of 1.17 for hemorrhage, and a minimum significant difference (0.8) between the two groups. Due to the possibility of patient withdrawal or loss to follow-up, 37 patients per group were selected during the predetermined data collection period.

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Received: 23 September 2018, Revised: 16 October 2018, Accepted: 29 October 2018

The authors declare no conflicts of interest.

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The patients were premedicated with midazolam (0.1 mg/kg) and ketamine (1.0 mg/kg) and transferred to the operating room where anesthesia was induced by the injection of atropine (0.02 mg/kg), fentanyl (2 µg/kg), propofol (2.0 mg/kg), and atracurium (0.5 mg/kg). Anesthesia was maintained with propofol infusion (200 µg/kg/min selected based on the recommended standard range of 150-300 µg/kg/min for children). The mentioned doses of atracurium and fentanyl were repeated every 20 minutes during the surgery.

Block randomization was used to allocate the patients to two groups. The first group received remifentanyl infusions (0.1 µg/kg/min) after the induction of anesthesia and the second group received an intravenous injection of tranexamic acid (10 mg/kg) before the beginning of the surgery.

Heart rate, mean arterial pressure (MAP), blood oxygen saturation (SpO₂), and end-tidal (ET) CO₂ levels were measured before the induction of anesthesia (baseline) and every 10 minutes during the surgery. Intraoperative blood loss was accurately recorded based on the amount of blood collected in the suction bottle and the number of blood-soaked gauzes (each full gauze was considered equivalent to 10 ml of blood). Surgeon's satisfaction was measured on a Likert scale at the end of each surgery.

The incidence of any complications, including hypotension (< 20% of baseline), hypertension (> 20% of baseline), and bradycardia/tachycardia (fall/rise of heart rate > 20% of baseline), were recorded during the surgery. The patients of both groups were also monitored for the mentioned complications and other problems, e.g. nausea and vomiting, decreased SPO₂, and laryngospasm/bronchospasm, in the post-anesthesia care unit (PACU). The patients' duration of PACU stay was also recorded based on the modified Aldrete

scores and the data collected from the two groups were compared.

Chi-square test, t-test, and repeated measures analysis of variance (ANOVA) were used for data analysis. All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Results

This study examined two groups of children (n= 37 each) undergoing cleft palate repair. The mean age of the patients was 16.1 ± 7.9 months in the remifentanyl group and 16 ± 8 months in the tranexamic acid group (P = 0.97). The mean weight of the patients in the above-mentioned groups was 10.3 ± 3.5 and 9.8 ± 3.2 kg, respectively (P= 0.53). Boys constituted 56.8% and 48.6% of the remifentanyl and tranexamic groups, respectively (n = 21 and 18, respectively; P = 0.49). No serious hemodynamic complications causing medical intervention or patient withdrawal were observed during the surgeries.

As seen in (Table 1), the tranexamic acid group had a significantly higher mean heart rate than the remifentanyl group at the 30th-120th minutes of the surgery. Moreover, the patients' heart rates showed significant changes in both groups during the study period (P< 0.001). During the 15th-120th minutes of the surgery, MAP values were also significantly higher in the tranexamic acid group than in the remifentanyl group (P< 0.001). The mean SpO₂ and ETCO₂ values were not significantly different between the two groups during the study period. The mean blood loss was 76.46 ± 14.7 and 57.76 ± 14.16 ml in the remifentanyl and tranexamic acid groups, respectively (P< 0.001). The mean PACU stay times were 64.5± 5.3 and 46.35 ± 4.4 min in the remifentanyl and tranexamic acid groups, respectively (P<0.001) (Table 2).

Table 1-The mean values of hemodynamic parameters in the two groups

Time	Heart rate			Mean arterial pressure		
	Tranexamic acid	Remifentanyl	P	Tranexamic acid	Remifentanyl	P
Pre-anesthesia	134.6±10.4	135.4±10.3	0.075	65.5±5.3	64.9±5.4	0.086
Post-anesthesia	132.6±10.1	132.2±10.2	0.087	64.1±5.3	63.4±5.2	0.055
15 min	131.7±10.1	127.6±9	0.07	63.5±5.4	59.1±4.5	<0.001
30 min	131.3±11.5	124.9±8.8	0.009	63.3±5.9	57.2±3.7	<0.001
45 min	131.4±11.9	123.7±9.3	0.003	61.1±11	56.1±3.6	0.001
60 min	130.5±13	122.2±9.6	0.002	62.5±6.2	55.4±3.4	<0.001
75 min	129.9±12.9	120.6±9.2	0.001	61.7±9.5	54.7±3.2	<0.001
90 min	129.3±13.1	9.5 ± 119.4	0.001<	62.5±6.3	54.4±3.1	<0.001
105 min	129.2±13.5	118.4±9.2	0.001<	62.5±6.3	54.1±3.3	<0.001
120 min	127.2±17.1	118.2±9.4	0.006	63.3±6.8	54.1±3.3	<0.001
P	0.009	<0.001	0.034	0.032	<0.001	<0.001

Table 2- The mean blood loss and duration of recovery stay

Variable	Group		P
	Remifentanyl	Tranexamic acid	
Blood loss (ml)	76.46±14.7	57.76±14.6	<0.001
Post-anesthesia care unit stay time (minute)	64.59±5.3	46.35±4.4	<0.001

The surgeon was satisfied and fully satisfied with respectively 13 and 24 surgeries (35.1% and 64.9%) in the tranexamic acid group. The corresponding values were respectively 14 and 23 (37.8% and 62.2%) in the remifentanyl group. No cases of dissatisfaction were recorded in either groups and the two groups had no significant difference in the overall satisfaction of the surgeon ($P=0.81$).

Six cases of intraoperative complications, including three cases of hypoxia and three cases of laryngospasm (8.1% and 8.1%, respectively), were observed in the tranexamic acid group. Ten cases of intraoperative complications, including eight cases of hypoxia and two cases of laryngospasm (21.6% and 5.4%, respectively) were seen in the remifentanyl group. Although the number of complications was higher in the remifentanyl group, the two groups had no significant differences in the incidence of complications ($P=0.28$).

Discussion

Intraoperative bleeding is a serious challenge in various surgical procedures. It is associated with relatively high mortality and morbidity, especially in pediatric procedures, such as cleft palate repair. Despite serious efforts to minimize the amount of bleeding in pediatric surgery, a unique and ideal method has not been proposed to date. Controlled hypotension, performed through the continuous infusion of fentanyl, is an approach to decrease intraoperative bleeding [5-6]. However, since remifentanyl is an opioid, it is not indicated in all patients and can increase the risk of several complications such as decreased SpO₂. Meanwhile, some studies have reported the relatively high effectiveness of tranexamic acid in preventing bleeding during various surgeries. However, no previous studies have compared the effects of tranexamic acid and controlled hypotension with remifentanyl during cleft palate repair. Therefore, the effects of these two methods were investigated and compared in this study.

In this study, there were no significant differences between the two groups in terms of demographic and baseline characteristics. Therefore, these factors had no confounding effects on the patients' hemodynamic status, bleeding volume, and incidence of intra- and post-operative complications. The differences observed between the two groups could hence be attributed to the type of drug administered to reduce bleeding.

The evaluation of intraoperative hemodynamic parameters showed higher heart rate and blood pressure in the tranexamic acid group than in the remifentanyl group. However, the two groups had no significant differences in the mean SpO₂ and ETCO₂ at all times. Furthermore, none of the patients in any of the two groups demonstrated serious intraoperative hemodynamic complications requiring medical interventions or patient withdrawal.

According to our findings, lower intraoperative blood loss was observed in the tranexamic acid group compared to the remifentanyl group. In a previous study by Roin et al, the effects of remifentanyl and tranexamic acid in reducing

intraoperative blood loss were examined. They compared the effects of two different doses of tranexamic acid (10 and 15 mg/kg) with placebo on blood loss during bilateral total knee arthroplasty and found the higher dose of tranexamic acid (15 mg/kg) to significantly decrease bleeding compared to the other two groups (462, 678, 918 ml in tranexamic acid 15, tranexamic acid 10, and placebo groups, respectively; $P<0.01$) [9]. In a review of 15 clinical trials, Zhang and colleagues concluded that the use of tranexamic acid could decrease bleeding during knee joint and hip arthroplasty by 500 ml [10]. Nevertheless, these studies evaluated the effects of tranexamic acid on blood loss in knee joint surgery in adults and no similar studies have compared the effects of tranexamic acid and controlled hypotension with remifentanyl on blood loss during pediatric cleft palate repair. Considering the limitations of our study, e.g. small sample size and predetermined tranexamic acid dosage, further studies on this subject are required.

Conclusion

Based on our findings, tranexamic acid is more effective than remifentanyl in decreasing intraoperative blood loss and PACU stay.

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