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Comparison of the effects of tranexamic acid, nitroglycerin, and remifentanil on the prevention of bleeding during herniated lumbar intervertebral disc surgery: A randomized clinical trial

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Abstract

Background:

Surgery is a well-known and effective method of treating lumbar intervertebral disc herniation. The present study aimed to compare the effects of administering tranexamic acid (TXA), nitroglycerin (NTG), and remifentanil (REF) on hemorrhage prevention during herniated lumbar intervertebral disc surgery.

Methods:

A double-blind clinical trial was conducted on 135 participants undergoing lumbar intervertebral disc surgery. A randomized block design was used for subject assignment to three groups including TXA, NTG, and REF. The hemodynamic parameters, bleeding rate, hemoglobin level, and the amount of infused propofol were measured and recorded after surgery. Data were then analyzed in SPSS software using Chi-square test and analysis of variance.

Results:

The mean age of participants in the study was 42.12 ± 7.93 years, and all three groups were equal in terms of demographic characteristics ($P > 0.05$). The mean arterial pressure (MAP) of the TXA and NTG groups was notably higher than the REF group ($P < 0.008$). The mean heart rate (HR) of the TXA and NTG groups was notably higher than the REF group ($P < 0.05$). The propofol dosage used in the TXA group was higher than the two groups of NTG and REF ($P < 0.001$).

Conclusion:

Among participants undergoing lumbar intervertebral disc surgery, the greatest MAP variability was observed in the NTG group. Higher mean HR and propofol consumption was observed in the NTG and TXA groups when compared to REF. No statistically significant differences were noted between groups in oxygen saturation or bleeding risk. Based on

these findings, REF may be considered a preferred surgical adjunct over TXA and NTG during lumbar intervertebral disc surgery.

Keywords: Bleeding time, hemorrhage, lumbar disc disease, nitroglycerin, remifentanil, tranexamic acid

INTRODUCTION

Surgery is a well-known and effective method of treating lumbar intervertebral disc herniation that may cause hemodynamic instability and limited visual access for the surgeon due to bleeding.[1] Hemorrhage-associated complications include diminished capacity for oxygen transport, decreased blood pressure and cardiac output, decreased perfusion in vital organs, limiting the surgeon's vision of the surgical field, increasing the operation duration, and the possibility of damaging the sensitive organs around the surgery site.[1,2,3] In spine surgeries, due to the adjacency of important and fragile nervous structures, controlling the bleeding facilitates the operation and decreases the operation duration, which further decreases bleeding risk.[1,2,3] Clonidine, dexmedetomidine, nitroglycerin (NTG), tranexamic acid (TXA), and remifentanil (REF) are some of the commonly used drugs to manage bleeding in surgeries.[4,5]

TXA is synthetically derived from lysine and acts as an antifibrinolytic agent which bonds to plasminogen and prevents its interaction with fibrin, which ultimately prevents the lysis of fibrin clots.[6,7,8] TXA is used to decrease hemorrhage in cardiac surgeries, and to treat idiopathic menorrhagia as well.[3,9,10,11,12]

NTG is metabolized in the liver and transformed into nitric oxide, a potent vasodilator which causes expansion and loosening of smooth muscle cells in vascular structures.[13] REF, a phenylpiperidine derivative, is a short-acting opioid analgesic which is widely used in

general anesthesia for its unique pharmacokinetic properties. High doses of REF may be administered during surgical procedures to improve hemodynamic stability, with no evident impact on the duration of recovery from the state of general anesthesia.[14,15,16] Patients who receive REF have lower systolic and diastolic blood pressures during surgery, which can be beneficial in the management of surgery-related hemorrhage.[14,16] In spine surgeries, it is crucial for the surgical field to have very little or optimally no hemorrhage at all, in order for the procedure to be performed with better visual access. Therefore, the primary and secondary outcome of this study was comparing the bleeding amount and hemodynamic parameters among the studied groups.

METHODS

A double-blind randomized clinical trial was conducted in patients undergoing lumbar intervertebral disc herniation surgery at an academic Medical Center in Iran from May 16, 20121 to April 30, 2022. The study was approved by the Institutional Ethics Committee, and registered prospectively with the Iran Clinical Trials Registry. Informed written consent was required for participants before study enrollment, and the manuscript adheres to the PRISMA guideline.

The participants were randomly divided into three groups using blocks of 6 that were generated using a dice roll. Groups were labeled in a de-identified fashion (A, B, and C) and concealment was maintained by study medications being similar in color, consistency, volume, and packaging. All study participants, investigators, clinical providers, and data abstractors remained blinded to the group of randomization. The statistician worked from a de-identified data set and thus was also blind to the group of randomization for individuals.

The study inclusion criteria were: an age restriction of 18–60 years old, American Society of Anesthesiologists Class II or lower, no evidence of active bleeding disorders, no history of cardiovascular diseases, no pregnancy, and no allergy to the three drugs used in the study. Exclusion criteria were: patient's lack of consent to surgery, opioid dependence, plasma creatinine level of >1.5 mg/dl, platelet count of <150,000/ml, body mass index (BMI) >35, and history of thromboembolism. To collect and evaluate the data, a checklist was used and data were collected by clinical provider and intern student.

Intervention

After documenting the demographic data, on entry at the operation room, two separately located intravenous lines were inserted; one for administering the drugs being studied, and another for administering intravenous liquids or other drugs. Then, at the beginning of the induction, 5 ml/kg of crystalloid liquid (ringer serum) was administered, and the patient's received oxygen at a 100% concentration level through oxygen masks. After that, 30 μg/kg of midazolam and 2 μg/kg of fentanyl were intravenously injected as premedication. Anesthesia induction was then performed by injecting 2.5 μg/kg of propofol and 0.5 μg/kg of atracurium, and the patients were intubated using an appropriately sized tracheal tube. Then, the patients were put under mechanical ventilation, to keep their expiratory CO_2 concentration level at 30–35 mmHg, and their blood oxygen saturation at 98%. To maintain the state of general anesthesia, oxygen and nitrous oxide (with a 50:50 ratio), as well as 1% isoflurane were administered until the end of the operation, and 10 mg of atracurium was administered intravenously every 20–30 min. Propofol infusion was also started at 50–150 μg/kg/min to stabilize the state of anesthesia and create controlled hypotension, which means lowering the mean arterial pressure (MAP) by 20%–30% of its initial

amount. Then, the patients were put into three groups using a randomized block design.

In each group, the specific drug being studied was administered in bolus and infused manners. After anesthesia induction and intubation and before the beginning of the operation, the bolus dose of the intervention drug of each group was calculated, and then, they were diluted to reach a 10 ml volume and were injected in 10 min. After that, their infusion dose was calculated and administered using an injection pump, and continued until the end of the operation.

Remifentanil group

As a bolus dose, 10 ml of normal saline was administered within 10 min, and then an infusion dose of 0.1 μg/kg/min was administered all through the surgery.[15]

Tranexamic acid group

Before making the surgical incision, a bolus dose of 10 mg/kg of TXA was prepared and through dilution using distilled water, its volume was adjusted at 10 ml to be slowly injected within 10 min. Then, an infusion dose of 2 mg/kg/h was administered throughout the operation (each 5 ml ampoule of TXA used in this study contained 500 mg of the drug).[9]

Nitroglycerin group

As a bolus dose, 10 ml of normal saline was administered in a 10-min period, which was then followed by an infusion dose of 5 μg/kg/min of NTG (each 2 ml ampoule of NTG used in this study contained 10 mg of the drug).[17]

Heart rate (HR), MAP, and arterial oxygen saturation percentage were measured and recorded before and after anesthesia induction, during the controlled hypotension stage, every 15 min until the end of the operation, during the recovery period, and also 2, 4, and 6 h after surgery. The amount of bleeding at the surgery site was then determined by the surgeon, who was blind to the study groups and was not aware of the type of drug used on each patient and rated from 0 to 5. Scoring varied from 0 as no hemorrhage to 5 as severe, unmanageable hemorrhage.[16,18] In this rating scale, any point equal or below 2 is considered desirable. The surgeon's satisfaction score was recorded according to a 3-point Likert scale, in which 0 means “unsatisfying,” 1 means “moderately satisfying,” and 2 means “satisfying.” Extubation was performed based on the patient's respiratory capability and the normalization of airway reflexes, and the recovery time was evaluated and documented in the evaluation form, according to the Aldrete score table.[19] Any patient receiving a 9 or higher score was transferred to the admission ward. Hypotension (MAP <60 mmHg), was managed by decreasing the dose of anesthetic agents and increasing the amount of crystalloid infusion. For those patients who did not respond well to the aforementioned measures, 5 mg of intravenous ephedrine was administered intravenously. In cases of stable bradycardia (HR <50 bpm), 0.5 mg of atropine was administered intravenously. Postoperation side effects including nausea and vomiting, chills, bronchospasm, headache, dizziness, blurred vision, and sore throat were documented. Any other antihypertensive drug used during surgery on each patient was also documented in the patient evaluation form, and the patient receiving that drug was removed from the study. The patients’ hemoglobin level was measured and documented before and also 12 h after surgery.

Statistics

Considering the study power equal to 80%, and the error of the first type equal to 5%, the minimum sample size required for each study group was determined to be 45. Therefore, 135 patients were evaluated in this study. The data were analyzed using IBM® SPSS® version 20 (IBM Corp., Armonk, NY, USA) software. Chi-square test, paired sample *t*-test, and one-way analysis of variance (ANOVA) were also used to compare the three groups. A repeated measure ANOVA was used to analyze the course of hemodynamic indexes in the three groups.

RESULTS

One hundred and fifty-one potential patients were identified, of which six were excluded [Figure 1] and 131 were included in the final analysis. The mean participant age was 42.12 ± 7.93 years (range 22–58), and the mean BMI was 24.89 ± 2.25. The lowest and highest age among the participants was 22 and 58 years old, respectively. Of the 135 participants, 51% were male, and since all three groups were matched in terms of age and sex distribution, no statistically significant difference was evident among them ($P > 0.05$). Comparing the mean age and BMI data in three groups revealed that the three groups did not have statistically significant differences regarding their age ($P = 0.0872$) and BMI ($P = 0.996$) and were matched in these variables ($P > 0.05$).

MAP [Table 1] of the patients of the three study groups revealed no statistically significant difference in the amounts recorded until 150 min after anesthesia induction. However, from recovery until 6 h after surgery, notable statistical differences were recorded ($P < 0.008$). *Post hoc* analysis indicated that the MAP of the patients of the TXA and NTG groups was significantly higher than that of the REF group. The MAP in the TXA group appeared to be higher than that of the NTG group. Repeated measures ANOVA [Figure 2] showed statistically significant differences among the three study groups; the highest rate of fluctuation

in MAP was observed in the NTG group, which was significantly different compared to the TXA and REF group ($P = 0.031$).

Comparing the mean HR [Table 2] of the patients of the three study groups indicated no statistically significant difference in the recorded amounts until 90 min after anesthesia induction ($P < 0.05$); however, after that, statistically significant differences were recorded among the three study groups ($P > 0.05$). Tukey's test results showed that the mean HR of the patients in the TXA and NTG groups was significantly higher than in the REF group ($P < 0.05$), although no statistically significant difference was noted between the TXA and NTG groups ($P > 0.05$). Repeated measures ANOVA [Figure 3] showed statistically significant differences in the course of mean HR of the three study groups, indicating that the recorded mean HR in all the checkpoints, both during and after surgery, was lower in the REF group compared to the other two groups ($P = 0.013$).

Comparing the mean SpO_2 of the patients in the three study groups [Table 3] showed that no statistically significant difference was recorded, neither during nor after surgery ($P > 0.05$).

The mean recovery time for patients to reach an Aldrete score of above 9 was calculated to be 154.20 ± 6.30 min, and the mean surgery duration was equal to 127.74 ± 5.19. One-way ANOVA [Table 4] indicated no statistically significant difference in the mean of time to extubation, mean recovery time and mean surgery duration among the participants in the three study groups ($P > 0.05$).

Mean bleeding rate, surgeon's satisfaction score, and the consumed propofol dosage of the three study groups revealed no significant difference in terms of mean bleeding rate and surgeon's satisfaction score in the three groups ($P < 0.05$). Whereas, the amount of consumed

propofol was notably different across the three study groups, and Tukey's test indicated that it was higher in the TXA group compared to the NTG and REF groups. The mean amount of consumed propofol was also higher in the NTG group in comparison to the REF group ($P < 0.001$).

Comparing the baseline level of hemoglobin to its level at 12 h after surgery in the three study groups [Table 5] suggested that there was no statistically significant difference between them. Nevertheless, there was a statistically significant difference in the baseline hemoglobin level compared to its level at 12 h after surgery, and the mean hemoglobin level had decreased in all three study groups ($P < 0.001$). Evaluation of the incidence rate of postsurgery headache in the patients across the three study groups indicated that with 8.9%, the REF group had the highest percentage among the three study groups; however, overall, no statistically significant difference was observed between the three groups ($P = 0.898$).

DISCUSSION

Studies showed that administration of TXA results in the reduction of bleeding during surgical procedures.[20] In 2014, Ghodraty *et al*., and in 2017, Matsuura *et al*. stated that administering REF leads to the reduction of bleeding during surgery.[15,16] In 2019, Ruku *et al*. stated that NTG can reduce hemorrhage in spine surgeries.[17]

In the present study, the MAP from recovery to 6 h after surgery is significantly higher in the TXA and NTG groups, compared to the REF group. Furthermore, the patients' mean HR, from 90 min after anesthesia induction until 6 h after surgery, is higher in the TXA and NTG groups, compared to the REF group. Our study indicated that there was no statistically significant difference in the amounts of mean SpO_2, mean extubation time, recovery time, and surgery duration in comparing the

TXA, NTG, and REF groups to each other. In this study, the highest amount of consumed propofol was recorded in the TXA group, the NTG group and the REF group, respectively.

Similar studies, unlike ours, have proven the relative superiority of magnesium sulfate to REF. For instance, in a study conducted by Modir *et al*., they showed that compared to dexmedetomidine, REF is less effective in lowering the bleeding rate.[21] Furthermore, in a study carried out by Bahramsari *et al*., it was concluded that dexmedetomidine had better effects on hemodynamic parameters compared to REF.[22] However, the protective effect of dexmedetomidine on the reduction of bleeding was not compared in their study groups. In other studies, including one conducted by Yazdi *et al*., administering the combination of REF and propofol did not create much change in the hemodynamic indexes.[23]

In the present study, the most recorded fluctuations in the amount of MAP belong to the NTG group. In a study by Ruku *et al*.[17] showed that administering 1 μg/kg/min of dexmedetomidine for 10 min before anesthesia induction, and infusing 0.2–0.7 mg/kg/h of it during surgery, had a better impact on blood pressure and HR, compared to administering an infusion of 3–10 μg/kg/min of 0.01% NTG, or administering 500 μg/kg of esmolol as a loading dose, 1 min before anesthesia induction, and infusing 50–300 μg/kg/min of it during the operation. They also stated that after dexmedetomidine, NTG had better effects on bleeding management, compared to esmolol.[17]

Our study showed that the mean bleeding rate, surgeon's satisfaction score, and hemoglobin level had no statistically significant difference among the three study groups. In the present study, no placebo comparison has been made, and the intervention groups have been compared only to each other. In this term, no difference was observed among the three groups; although in all of them, the bleeding rate had

decreased during surgery, which meant that our interventions in all of the study groups had protective effects on bleeding during surgery. Therefore, the lack of statistically significant difference across our study groups in the present study is because of the absence of a placebo group to be compared with the intervention groups. Nagabhushan *et al*. showed that administering batroxobin with the combination of batroxobin and TXA was proven to be useful in reducing hemorrhage during surgery.[3] In a study by Matsuura *et al*. which aimed to investigate the effects of REF on reducing hemorrhage during orthognathic surgery, it was concluded that administering an infusion of REF at 0.05–0.25 μg/kg/min reduced bleeding but had no impact on reducing the patients' blood pressure.[15] In another study conducted by Colomina *et al*. in 2017, it was noted that administering 10 mg/kg of TXA before making the surgical incision, and infusing 2 mg/kg/h of it throughout the operation reduced overall blood loss and also the bleeding during surgery, but did not decrease the need for blood transfusion.[9] Furthermore, in 2 other studies, the effect of TXA on reducing bleeding was observed. In a study by Sankar *et al*., administering an initial dose of 10 mg/kg of TXA, followed by 1 mg/kg of it as a maintenance dose, compared to administering normal saline, reduced the bleeding and provided more visual clearance at the surgery site.[20] Furthermore, Cheriyan *et al*. showed, in a review article, that TXA reduces bleeding during surgery and also reduces the need for blood transfusion in patients undergoing spine surgery, without increasing the risk of thromboembolism, *deep vein thrombosis*, or Myocardial infarction (MI).[24]

CONCLUSION

Among participants undergoing lumbar intervertebral disc surgery, the greatest MAP variability was observed in the NTG group. Higher mean HR and propofol consumption was observed in the NTG and TXA groups

when compared to REF. No statistically significant differences were noted between groups in oxygen saturation or bleeding risk. Since, treatment with less variability in MAP, lower HR, without change in SpO2 and lower bleeding risk would indicate a favorable regimen, therefore, based on these findings, REF may be considered a preferred surgical adjunct over TXA, followed by NTG, during lumbar intervertebral disc surgery.

Research quality and ethics statement

This study was approved by the Institutional Review Board at Arak University of Medical Sciences (Approval #IR.ARAKMU.REC.1399.351; Approval date March 7, 2021). The authors followed the PRISMA guideline, and the study was registered prospectively with the Iranian Registry of Clinical Trials (IRCT20141209020258N159).

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Figure 1

PRISMA flow chart diagram. NTG: Nitroglycerin, REF: Remifentanil, TXA: Tranexamic acid

Table 1

Comparing the mean arterial pressure of the patients of the three study groups of tranexamic acid, nitroglycerin, and remifentanil

	Mean±SD			
MAP				***P***
	NTG	**REF**	**TXA**	
Before intervention (baseline)	93.64±5.01	93.58±4.88	93.80±5.30	0.977
15 min after anesthesia induction	91.62±5.02	91.58±4.88	91.84±5.34	0.965

MAP	Mean±SD			*P*
	NTG	**REF**	**TXA**	
30 min after anesthesia induction	90.67±4.97	90.58±4.90	90.84±5.34	0.968
45 min after anesthesia induction	89.64±5.00	89.58±4.90	90.84±5.34	0.415
60 min after anesthesia induction	89.42±4.74	89.31±4.82	90.78±5.33	0.300
75 min after anesthesia induction	89.18±4.81	89.27±4.76	90.69±5.28	0.271
90 min after anesthesia induction	89.42±4.74	89.31±4.82	90.78±5.33	0.300
105 min after anesthesia induction	89.00±4.61	89.04±4.65	90.69±5.38	0.180
120 min after anesthesia induction	88.73±4.48	89.96±4.66	90.64±5.41	0.130
135 min after anesthesia induction	88.29±4.36	88.67±4.51	90.60±5.44	0.053
150 min after anesthesia induction	89.84±3.63	89.58±4.69	91.33±5.10	0.143
Recovery	94.64±2.54	92.11±4.22	92.84±4.63	0.008
2 h after surgery	95.64±2.33	92.38±4.02	93.22±4.38	<0.001
4 h after surgery	96.24±2.23	92.64±4.02	92.78±3.91	<0.001
6 h after surgery	96.44±2.29	92.78±3.91	94.60±5.10	<0.001

MAP: Mean arterial pressure, NTG: Nitroglycerin, REF: Remifentanil, TXA: Tranexamic acid, SD: Standard deviation

Figure 2

Comparing the course of MAP in the patients of the three study groups. MAP: Mean arterial pressure

Table 2

Comparing the mean heart rate of the patients of the three study groups of tranexamic acid, nitroglycerin, and remifentanil

HR	Mean±SD			*P*
	NTG	**REF**	**TXA**	
Before intervention (baseline)	92.73±5.45	92.71±5.30	92.72±5.48	0.999
15 min after anesthesia induction	92.62±5.37	92.02±5.04	92.56±5.48	0.841
30 min after anesthesia induction	92.49±5.25	91.53±4.76	92.42±5.41	0.618

HR	Mean±SD			*P*
	NTG	**REF**	**TXA**	
45 min after anesthesia induction	92.40±5.23	91.36±4.41	92.33±5.33	0.543
60 min after anesthesia induction	92.31±5.08	90.84±4.22	92.18±5.18	0.287
75 min after anesthesia induction	92.07±4.94	90.42±3.96	92.07±5.14	0.165
90 min after anesthesia induction	91.89±4.89	89.96±3.77	91.93±5.05	0.071
105 min after anesthesia induction	91.78±4.87	89.49±3.60	91.78±5.06	0.025
120 min after anesthesia induction	91.62±4.82	89.31±3.52	91.67±5.07	0.021
135 min after anesthesia induction	91.60±4.89	89.04±3.60	91.67±5.07	0.010
150 min after anesthesia induction	92.89±4.50	90.18±3.87	92.75±4.58	0.005
Recovery	93.80±4.09	91.93±3.97	93.47±4.48	0.045
2 h after surgery	94.53±2.98	92.84±3.55	94.36±3.20	0.028
4 h after surgery	95.04±2.89	93.42±3.09	94.91±3.22	0.023
6 h after surgery	95.31±2.71	93.87±2.86	95.38±2.76	0.016

HR: Heart rate, NTG: Nitroglycerin, REF: Remifentanil, TXA: Tranexamic acid, SD: Standard deviation

Figure 3

Comparing the course of mean HR in the patients of the three study groups. HR: Heart rate

Table 3

Comparing the mean blood oxygen saturation of the patients in the three study groups of tranexamic acid, nitroglycerin, and remifentanil

SpO_2	Mean±SD			*P*
	NTG	**REF**	**TXA**	
Before intervention (baseline)	97.69±0.557	97.65±0.559	97.68±0.556	0.999
15 min after anesthesia induction	97.69±0.557	97.68±0.596	97.68±0.557	0.999
30 min after anesthesia induction	97.71±0.589	97.71±0.589	97.67±0.603	0.919
45 min after anesthesia induction	97.73±0.580	97.71±0.626	97.73±0.580	0.979
60 min after anesthesia induction	97.73±0.580	97.73±0.618	97.73±0.580	0.999

SpO_2	Mean±SD			*P*
	NTG	**REF**	**TXA**	
75 min after anesthesia induction	97.73±0.581	97.73±0.618	97.72±0.582	0.999
90 min after anesthesia induction	97.78±0.560	97.80±0.661	97.84±0.562	0.864
105 min after anesthesia induction	97.78±0.560	97.80±0.661	97.84±0.562	0.864
120 min after anesthesia induction	97.73±0.562	97.84±0.562	97.82±0.614	0.979
135 min after anesthesia induction	97.84±0.562	97.82±0.614	97.82±0.576	0.979
150 min after anesthesia induction	97.82±0.576	97.71±0.589	97.69±0.596	0.394
Recovery	97.84±0.562	97.71±0.589	97.69±0.596	0.394
2 h after surgery	97.89±0.573	97.80±0.588	97.78±0.599	0.637
4 h after surgery	97.89±0.573	97.82±0.614	97.78±0.599	0.637
6 h after surgery	97.89±0.573	97.82±0.614	97.78±0.599	0.637

SpO_2: Blood oxygen saturation, NTG: Nitroglycerin, REF: Remifentanil, TXA: Tranexamic acid, SD: Standard deviation

Table 4

Comparing the mean extubation time, recovery time and surgery duration, the amount of hemorrhage, surgeon's satisfaction score, and the dose of propofol administered to the patients in the three study groups of tranexamic acid, nitroglycerin, and remifentanil

Variable	Mean±SD			*P*
	NTG	**REF**	**TXA**	
Extubation time (min)	135.18±4.44	135.20±5.57	135.18±4.81	0.999
Recovery time (Aldrete score ≥9)	154.22±5.96	154.16±6.11	154.22±6.93	0.998
Surgery duration	127.73±5.19	127.78±5.26	127.71±5.26	0.998
The amount of bleeding	1.16±0.37	1.16±0.37	1.22±0.560	0.710
Surgeon's satisfaction score	1.96±0.21	1.96±0.21	1.93±0.25	0.863
Administered propofol dosage	886.16±5.11	876.40±6.63	890.53±3.58	<0.001

NTG: Nitroglycerin, REF: Remifentanil, TXA: Tranexamic acid, SD: Standard deviation

Table 5

Comparing the mean level of hemoglobin at baseline and 12 h after surgery in the three study groups of tranexamic acid, nitroglycerin, and remifentanil

Hemoglobin level	**Mean±SD**			***P***
	NTG	**REF**	**TXA**	
Baseline hemoglobin level	13.61±0.52	13.61±0.48	13.61±0.49	0.994
Hemoglobin level 12 h after surgery	12.96±0.52	13.01±0.52	12.94±0.53	0.816
P (paired sample t-test)	<0.001	<0.001	<0.001	-

NTG: Nitroglycerin, REF: Remifentanil, TXA: Tranexamic acid, SD: Standard deviation