Original Article

Tranexamic Acid versus Hypotensive Anesthesia using Isoflurane for Improvement of Outcome of Functional Endoscopic Sinus Surgery

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Objectives: ***To evaluate applicability of tranexamic acid (TXA) infusion with normotensive anesthesia in comparison to hypotensive anesthesia during functional endoscopic sinus surgery (FESS).***

Patients & Methods: ***The study included 70 patients allocated into two equal groups: Group H received hypotensive anesthesia and Group N received normotensive anesthesia. Anesthesia was maintained in both groups by isoflurane 1-2%, but in group H, MAC of isoflurane was adapted to maintain mean arterial blood pressure (MAP) values in range of 60-70 mmHg. In group N, 500 mg TXA (loading dose) was given 20 minutes before surgery followed by continuous TXA infusion (1 mg/kg/min) till the end of surgery. Operative field bleeding and its visibility was graded using 6-point scale. For both groups, tranexamic acid (4 gm) was given if bleeding score was ≥3. Total amount of bleeding and operative times were recorded.***

Results: ***All patients had smooth intraoperative course without uneventful events. Mean operative time was significantly longer in group H compared to group N. All patients had bleeding score in range of 1-4 with significantly higher scores in group H compared to group N. The frequency of patients had low bleeding score was significantly higher in group N compared to group H. Mean amount of intraoperative blood loss was significantly higher in group H compared to group N. Mean dose of tranexamic acid used in group N was 5.88±1.1; range: 3.9-7.8 gm. Thirteen patients (18.6%) required booster dose of tranexamic acid; 9 in group H and 4 in group N with significantly lower need in group N.***

Conclusion: ***The applied regimen of TXA administration during FESS significantly minimized intraoperative bleeding, and improved surgical field visibility with subsequent significant reduction of operative time. Moreover, it spared the need for hypotensive anesthesia with its consequent hemodynamic changes and costs.***

Keywords: ***Tranexamic acid infusion, FESS, Hypotensive anesthesia, Bleeding scores.***

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common condition; its precise incidence is difficult to estimate due to discrepancies in its definition. It is generally defined as the presence of two or more sino-nasal symptoms, one of which includes nasal obstruction, nasal blockage, congestion or nasal discharge with or without facial pain, facial pressure and reduction of smell or loss of smell for a period of over 12 weeks. Endoscopic evidence of pus and/or oedema and CT scan findings of blocked osteomeatal patency helps in confirming diagnosis.[1-3]

Medical therapy is the primary treatment modality for patients with CRS rhinosinusitis in the form of antibiotics and topical nasal steroids. However, CRS not responding to medical treatment and nasal polyposis are two classical indications for performing endoscopic sinus surgery. Functional endoscopic sinus surgery (FESS) is a set of minimally invasive techniques in which sinus air cells and ostia are opened under direct visualisation. With FESS, the advantage of good illumination and clear vision with minimally invasive surgery, it is possible to achieve consistently good results, provided the surgery is done accurately and with care. Recently, image guided operating room equipped with image guided systems and CT scanning, which can reflect anatomic changes during surgery, carrying the promise of increased safety.[4,5]

Operative field visibility is a major determinant for FESS outcome; increased bleeding during surgery interfere with operative field visibility and undoubtedly lead to occurrence of complications or causes finishing surgeries before the due time, when targets raised at the beginning are given up in order to avoid possible complications. Improvement of intraoperative visibility, while reducing bleeding is an important challenging task for both the anesthetist and otorhinologist.[6,7]

Numerous interventions are performed with general anesthesia for FESS aiming at reduction of intraoperative bleeding and improvement of field visibility. Hypotensive anesthesia is one modality for control and reduction of bleeding during surgery. The state of "hypotension" was achieved by reducing the peripheral blood vessel resistance, reducing the heart volume per minute and by inter-coordinating these two effects. Most frequently peripheral vasodilators, beta-blockers, volatile anesthetics are used to cause induced hypotension.[8-10]

Reduction of operative blood loss can be achieved by either enhancement of fibrin formation through activation and promotion of coagulation cascade or by providing more fibrinogen. Another strategy is to decrease degradation of fibrin by inhibiting the conversion of plasminogen to plasmin which is responsible for fibrin degradation. Pharmacologic diminution of fibrinolytic activity can be achieved with the relatively specific synthetic lysine analogs tranexamic acid (TXA) which blocks the lysine-binding sites on plasminogen, thereby preventing its activation to plasmin. TXA is the most promising antifibrinolytic due to a favorable benefit-risk ratio, the 10 times lower dose required than with epsilon aminocaproic acid and the high safety profile depending on experience from several decades of use for most types of bleeding or surgery in patients with congenital or acquired bleeding disorders.[8-10]

The current prospective study aimed to evaluate the outcome of FESS surgery using either tranexamic acid regimen of loading dose followed by TXA infusion in conjunction with normotensive anesthesia or hypotensive anesthesia using isoflurane as two modalities for reduction of intraoperative bleeding.

PATIENTS AND METHODS

The current study was conducted at Departments of Otorhinolaryngology and Anesthesia, Doha Clinic Hospital, Doha, Qatar during the period from January 2012 till June 2013. After approval of the study protocol by the local Ethical Committee and obtaining fully informed written patients' consents, all patients assigned for FESS were included in the study. Seventy patients were randomly, using sealed envelopes, allocated into two equal groups Group H (n=35) included patients assigned to receive hypotensive anesthesia and Group N (n=35) included patients assigned to receive normotensive anesthesia.

Patients with cardiovascular disease, hypertension, bleeding diathesis and those administering aspirin or other medications affecting coagulation system and patients with kidney or liver dysfunctions, as well as anemia (Hb<10g/dl) were excluded off the study.

All patients were pre-medicated with midazolam (0.05 mg/kg), 2 min thereafter, anesthesia was induced by a bolus of remifentanil (1 µg/kg) followed by propofol (1-2 mg/kg) and vecuronium was given in dose of 1 mg/kg to facilitate tracheal intubation followed by maintenance doses of 10-20 mg. Anesthesia was maintained in group N by isoflurane 1-2%. However, in group H, MAC of isoflurane was adapted according to hemodynamic responses, in order to maintain mean arterial blood pressure (MAP) values in the range of 70-80 mmHg. In group N, a loading intravenous dose of 500 mg tranexamic acid (TXA) was given 20 minutes before surgery followed by continuous TXA infusion at rate of 1 mg/kg/min till the end of surgery.

Immediately after tracheal intubation, middle meatus packing was conducted, under endoscopic guidance, using adrenaline (1:100,000) soaked pledgets to obtain maximum contraction of the mucosa and thus better visualization of the main features of the meatus. After 5 minutes, the pledgets were removed, xylocaine (1%) with adrenaline (1:100,000), 1-1.5 ml, was injected under the mucosa of the uncinate process, at the level of the head of the middle turbinate and the inferior part of the bulla. Local anesthetic was given at the point of insertion of the middle turbinate, so as to block the branches of the anterior ethmoidal nerve.

Throughout operative procedure; heart rate, blood loss, systolic and diastolic blood pressures were non-invasively monitored and recorded before time of induction of anesthesia and every 5-minutes thereafter till end of

surgery and was expressed collectively every 15 minutes till end of surgery. Operative field bleeding and subsequently its visibility was graded using 6-point scale: 0= no bleeding, 1=slight bleeding not necessitating evacuation, 2=slight bleeding that sometimes needed to be evacuated, 3= low bleeding, blood has to be often evacuated and operative field is visible for some seconds after evacuation, 4=average bleeding, blood has to be often evacuated and operative field is visible only right after evacuation and 5=high bleeding and constant blood evacuation is needed but sometimes bleeding exceeds evacuation and surgery is hardly possible or impossible at al.[11] For both groups, a booster dose of tranexamic acid of 4 gm was given if bleeding score was ≥3. Total amount of bleeding as judged by the amount evacuated and operative times were also recorded.

Statistical analysis: Sample Power was calculated according to Kraemer & Thiemann[12] using the proposed figure showed the sample size for 60% power would require an N of 31/group and 80% power would require an N of 51/group. This hypothesis was documented by Murphy & Myors.[13] Thus the current study sample size was chosen to be 35 patients per group. Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Wilcoxon; ranked test for unrelated data (Z-test) and Chi-square test (X2 test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

RESULTS

The study included 70 patients; 49 males and 21 females with mean age of 33±6.2; range: 25-49 years. Mean body mass index (BMI) of enrolled patients was 32.7±1.7; range: 26.8-34.9 kg/m2. There was non-significant (p>0.05) difference studied groups as regards the constitutional data, (Table 1).

Table 1 Patients' demographic data and pre-anesthetic clinical grading

				Total	Group H	Group N	p value
Age (years)	Strata	25-30		27 (38.6%)	12 (34.3%)	15 (42.9%)	
		>30-35		27 (38.6%)	15 (42.9%)	12 (34.3%)	
		>35-40		1 (1.4%)	1 (2.8%)	0	>0.05
		>40-45		12 (17.1%)	5 (14.3%)	7 (20%)	
		>45		3 (4.3%)	2 (5.7%)	1 (2.8%)	
	Total			33±6.2 (25-49)	33.5±6.2 (26-49)	32.4±6.2 (25-47)	>0.05
Gender	Males			49 (65.3%)	24 (68.6%)	25 (71.4%)	>0.05
	Females			21 (.34.7%)	11 (31.4%)	10 (28.6%)	
Body mass data	Weight (kg)			91.5±5.9 (73-103)	91.4±6.4 (73-103)	91.6±5.4 (80-100)	>0.05
	Height (cm)			167.2±4.9 (158-180)	167.1±4.7 (159-180)	167.3±5.2 (158-180)	>0.05
	BMI (kg/m^2)	Strata	25-30	7 (9.8%)	3 (8.5%)	4 (11.4%)	>0.05
			>30-35	63 (90.2%)	32 (91.5%)	31 (88.6%)	
		Total		32.7±1.7 (26.8-34.9)	32.6±1.5 (27.5-34.9)	32.8±1.9 (26.8-34.9)	>0.05
ASA grade	I			56 (60%)	27 (77.2%)	29 (83.9%)	
	II			9 (25.7%)	5 (14.3%)	4 (11.4%)	>0.05
	III			5 (14.3	3 (8.5%)	2 (5.7%)	

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis; BMI: Body mass index; ASA: American Society of Anesthesiologists grading system

Mean preoperative hemodynamic data showed non-significant (p>0.05) difference between studied groups. Patients received hypotensive anesthesia (Group H) showed progressive decrease of heart rate with significant (p<0.05) difference compared to baseline till the end of surgery. On the other hand, HR of patients received normotensive anesthesia (Group N) showed non-significant (p>0.05) decrease compared to baseline HR till the end of the surgery. Patients of Group H showed significantly (p<0.05) lower HR compared to those enrolled in Group N, (Table 2).

Table 2 Mean (±SD) heart rate levels recorded throughout surgery in both groups

		Baseline	15-min	30-min	45-min	End of surgery
Group H	Mean±SD	83±3.5	77.1±3.1	70.6±3.4	65.9±3	72.7±3.2
	p_1		Z=5.225; <0.001	Z=5.191; <0.001	Z=5.176; <0.001	Z=5.167; <0.001
Group N	Mean±SD	81.1±4.1	81±4	78.9±3.1	78.5±4.3	79.7±5.1
	p_1		Z=0.754; >0.05	Z=1.187; >0.05	Z=1.524; p>0.05	Z=1.238; p>0.05
	p_2	Z=1.123; >0.05	Z=2.615; =0.009	Z=4.957; <0.001	Z=5.162; <0.001	Z=4.663; <0.001

Data are presented as mean±SD p1: significance versus baseline levels p2: significance versus group N

Patients of Group H showed progressive decrease of blood pressure measures with significant (p<0.05) difference compared to baseline till the end of surgery. In group N, patients showed significantly (p<0.05) lower blood pressure measures compared to baseline measures, however, at the end of surgery, mean blood pressure measures showed non-significant (p>0.05) decrease compared to baseline measures, (Table 3).

Table 3 Mean (±SD) blood pressure levels estimated throughout surgery in both groups

		Baseline	15-min	30-min	45-min	End of surgery
Group H	SAP	119.9±5.5	91±5.7	88.4±4.3	85.5±6.7	115.3±7.4
	p		<0.001	<0.001	<0.001	<0.05
	DAP	76.5±2.2	69.6±2.5	63.7±2.7	62.8±2.8	72.1±2.9
	p		<0.001	<0.001	<0.001	<0.05
	MAP	90±3.3	76.7±3.6	71.9±3.2	70.4±4.1	86.5±4.4
	p		<0.001	<0.001	<0.001	<0.01
Group N	SAP	122.7±7.3	118.2±6.1	115.3±7.1	116.6±8.8	119.7±11.3
	p		<0.05	<0.05	<0.05	>0.05
	DAP	74.9±2.8	72.6±2.2	68.4±2.6	65.6±2.9	71±2.3
	p		<0.05	<0.05	<0.05	>0.05
	MAP	90.8±4.3	87.8±3.5	84±4.1	82.6±4.9	87.6±6.3
	P		<0.05	<0.05	<0.05	>0.05

Data are presented as mean±SD; SAP: systolic blood pressure; DAP: diastolic blood pressure; MAP: mean blood pressure

All patients had smooth intraoperative course uneventfully. Mean operative time was significantly (Z=2.207, p=0.027) longer in group H compared to group N, (Fig. 1). No patient in both groups had bleeding score of zero or 5 and all were in range of 1-4 with significantly (Z=4.243, p<0.001) higher total bleeding score in group H compared to group N, (Fig. 2). The frequency of patients had low bleeding score was significantly (X2=7.322, p<0.01) higher in group N compared to group H, (Fig. 3). Mean amount of intraoperative blood loss was significantly (Z=4.150, p<0.001) higher in group H compared to group N, (Table 4, Fig. 4).

Mean dose of tranexamic acid used in group N was 5.88±1.1; range: 3.9-7.8 gm. Thirteen patients (18.6%) required booster dose of tranexamic acid; 9 in group H and 4 in group N with significantly (X2=6.712, p<0.01) lower need for booster dose of tranexamic acid in group N.

Table 4 Operative time and scoring of field visibility as judged by extent of intraoperative bleeding

			Group H	Group N	p
Operative time (min)			68.8±11.8 (50-95)	64.2±10.8 (45-85)	Z=2.208; =0.027
Intraoperative bleeding data	Scores	1	11 (31.4%)	20 (57.1%)	X^2=7.322; p<0.01
		2	15 (42.9%)	10 (28.6%)	
		3	6 (17.1%)	4 (11.4%)	
		4	3 (8.6%)	1 (2.9%)	
	Total score		2±0.9 (1-4)	1.5±0.8 (1-4)	Z=4.150; p<0.001
	Amount (ml)		189.2±34.8 (120-250)	151.6±30.6 (100-220)	Z=4.243; p<0.001

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis

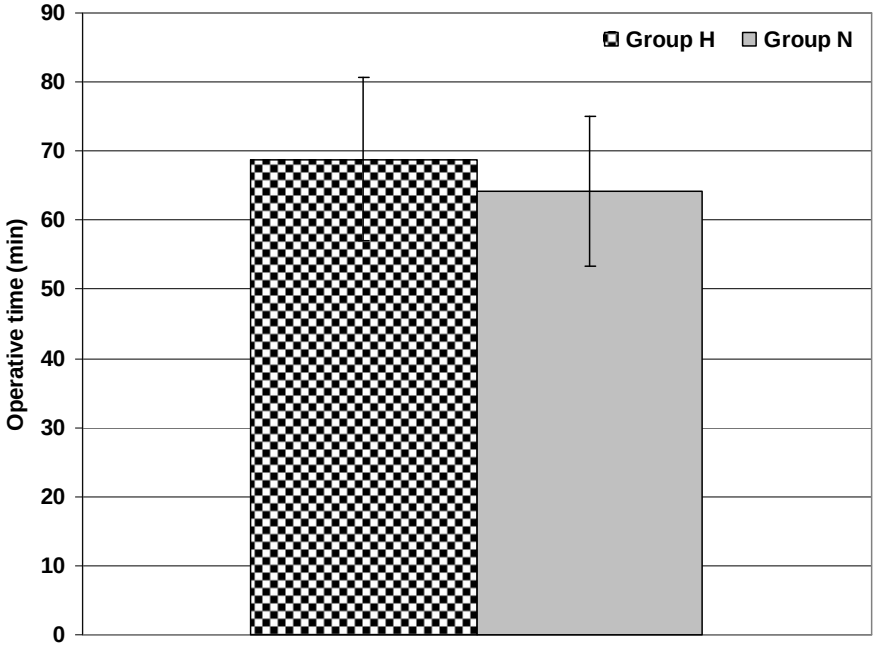

Fig. (1): Mean operative timefor both studied groups

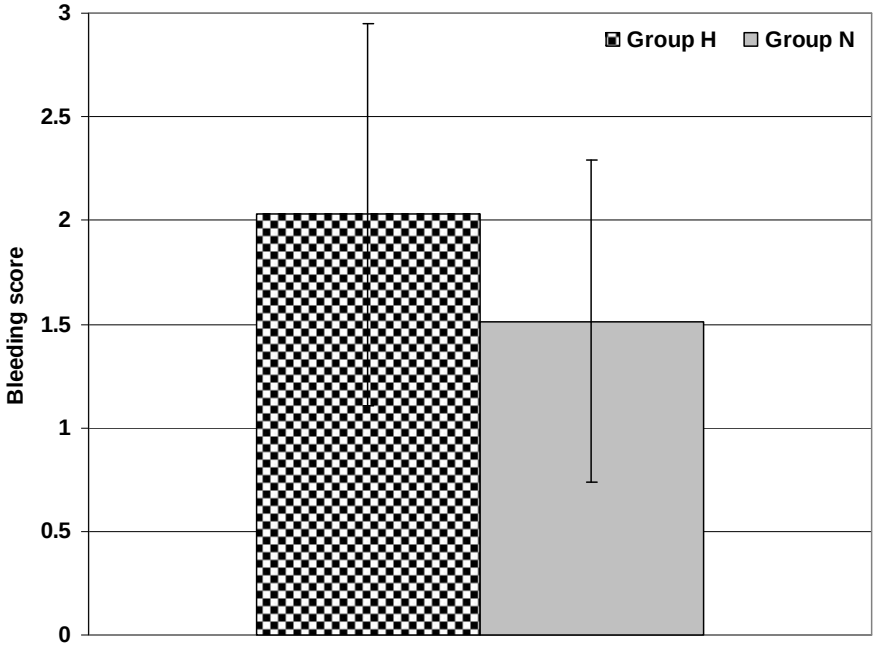

Fig. (2): Mean intraoperative bleeding score of patients of studied groups

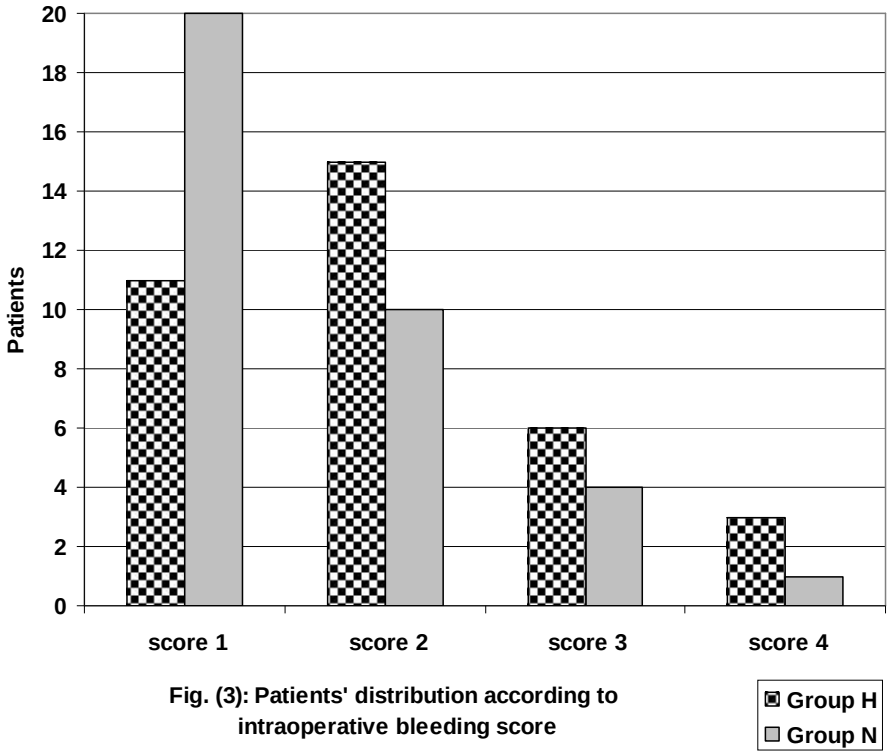

Fig. (3): Patients' distribution according to intraoperative bleeding score

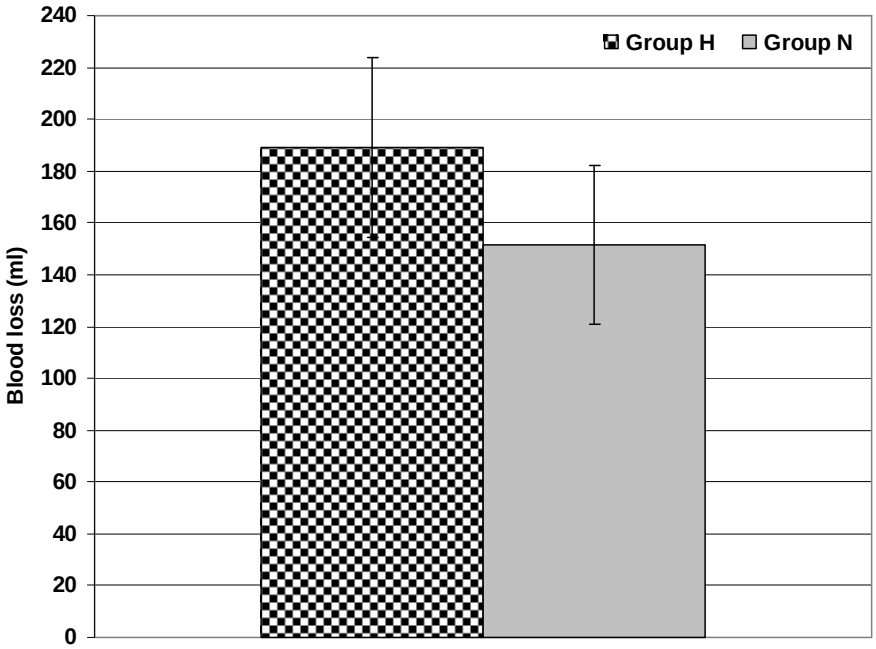

Fig. (4): Mean intraopertive blood loss recorded in studied groups

DISCUSSION

The applied policy for administration of tranexamic acid as priming by a loading dose 20 minutes prior to surgery and infusing a continuous infusion of 1 mg/kg/min and keeping a booster dose of 4 gm as one shoot if required approved efficacy during normotensive anesthesia during FESS surgery. Efficacy of such protocol was evidenced by the significantly lower amount of intraoperative bleeding, lower collective bleeding score with subsequent significantly better field visibility and significantly shorter operative time. Moreover, the frequency of patients required booster dose was significantly lower in group N compared to group H.

In line with the applied dosage policy used in current study; Reust et al.[14] using large pigs randomly assigned to receive TXA 30 mg/kg, diluted into 50 ml normal saline or 50 ml normal saline, microdialysis probes were placed in the liver, myocardium, kidney, and quadriceps muscle compartments and microdialysate infusion contained a validated plasmin-specific fluorogenic peptide, the fluorescence emission of the interstitial fluid collected from the microdialysis probes, which directly reflects plasmin activity was determined; TXA significantly reduced plasma plasmin activity at 30 min, TXA induced temporally distinct plasmin activity profiles within selected interstitial compartments and caused region-specific changes in plasmin activity profiles, and concluded that these temporal and regional differences in the effects of TXA may have important therapeutic considerations when managing fibrinolysis in the perioperative period.

Clinically, CRASH-2 collaborators[15] conducted a randomised controlled trial in 274 hospitals in 40 countries included 20 211 adult trauma patients with, or at risk of, significant bleeding randomly assigned within 8 h of injury to receive either tranexamic acid as a loading dose 1 g over 10 min then infusion of 1 g over 8 h or matching placebo and found that all-cause mortality was significantly reduced with tranexamic acid and the risk of death due to bleeding was also significantly reduced.

The reported efficacy of the applied policy goes in hand with that previously reported in literature concerning similar policies relied on tranexamic acid during various surgical modalities; Elwatidy et al.[16] compared TA and placebo given shortly after the induction of anesthesia as a loading dose of 2 g followed immediately by continuous infusion of 100 mg/h during surgery and for 5 hours after the operation and found that patients who received TA had 49% reduction of blood loss and required 80% less blood transfusion than patients who received placebo with shorter hospital stay and concluded that prophylactic use of TA provides an effective, safe, and cheap method for reducing blood loss during and after spinal operations. Iavorovskiĭ et al.[17] evaluated the efficacy of TXA given as a loading dose (15 mg/kg) and maintenance infusion (1 mg/kg/h) throughout the operation versus epsilon-aminocapronic acid (EACA) and reported that TXA has a 4-fold antifibrinolytic activity as compared with EACA manifested clinically as reduced blood loss volume during and after surgery and a lower frequency of use of donor blood elements and recommended TXA as one of the blood-preserving technology components during cardiosurgical operations under extracorporeal circulation.

Grant et al.[18] compared transfusion requirements for idiopathic scoliosis patients undergoing posterior only instrumentation and fusion receiving either a low (10 mg/kg loading, 1 mg/kg/h infusion) or high (20 mg/kg loading, 10 mg/kg/h infusion) dose of TXA and found high-dose TXA showed a trend toward a reduction in transfusion requirements compared with the low dose although this difference was underpowered to show a difference.

The reported data of the current study supported that previously reported concerning use of TXA in cases of otorhinolaryngological surgeries; Yaniv et al.[19] found TXA is a safe and effective drug for the reduction of bleeding in nasal surgery and recommended its routine use. Athanasiadis et al.[20] reported that topical application of TXA is effective in achieving hemostasis and improving the surgical field during FESS.

Patients received TXA either in group N as the sole therapy or in group has a booster doses did not show side effects or thrombotic complications. In line with safety of TXA, Liu et al.[21] reported that meta-analysis of literatures before November 2009 indicates that the use of TXA infusion for patients undergoing spine surgery is effective in reducing total blood loss, transfusion volumes and the rate of transfusion, yet doesn't raise the risk of postoperative DVT.

CONCLUSION

The applied regimen of tranexamic acid administration during FESS significantly minimized intraoperative bleeding, and improved surgical field visibility with subsequent significant reduction of operative time. Moreover, it spared the need for hypotensive anesthesia with its consequent hemodynamic changes and costs.

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