ORIGINAL RESEARCH PAPER

Anaesthesiology

KEY WORDS:

A COMPARATIVE STUDY OF TRANEXAMIC ACID AND EHAMSYLATE FOR CONTROL OF BLOOD LOSS IN FUNCTIONAL ENDOSCOPIC SINUS SURGERY

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INTRODUCTION

Functional endoscopic sinus surgery (FESS) is a highly sophisticated type of surgery which has revolutionized the surgical management of chronic sinus diseases(1).

Functional endoscopic sinus surgery is a minimally invasive procedure done to restore the natural mucociliary clearance mechanism, drainage and aeration of the sinuses while maintaining the normal anatomy as much as possible.

Major complications like optic nerve damage, damage to dura, cerebrospinal rhinorrhea, meningitis and even death has been reported for functional endoscopic sinus surgery (FESS) under general anesthesia as well as local anesthesia. This results from impaired visibility due to excessive bleeding during surgery[1]. These threats of serious complications from poor visibility due to excessive bleeding in the surgical field and the increased chances of neurological damage makes it important for the anaesthesiologists to produce optimal surgical conditions(2).

Bleeding occurs from intra bony vessels which are unsupported and capillaries which cannot be ligated(3). Antifibrinolysis and hemostasis are the two mechanisms which can be used for optimal surgical field without endangering life or wellbeing of the patient. The need for blood transfusion is also reduced.

Several techniques have been proposed for improvement of the surgical field in functional endoscopic sinus surgery. Bipolar diathermy, topical vasoconstrictors and induced hypotension are among the most frequently used(3,4). Of these, diathermy may result in local tissue damage and subsequent bleeding(3). Topical vasoconstrictors may result in hemodynamic instability, especially in patients with a history of hypertension or ischemic heart disease(5). Induced hypotension with volatile agents or narcotics exposes the patients to more anaesthetic drugs and consequently their side effects such as delayed recovery(2). Furthermore, none of these techniques are able to provide consistently a desirable bloodless field for the surgeon. Tranexamic acid and Epsilon-aminocaproic acid has also been used decrease bleeding and improve visualization of the surgical field during functional endoscopic sinus surgery(6). Hence to provide optimal field, hypotensive agents such as sodium nitroprusside (SNP), nitroglycerine (NTG), propofol, clonidine, inhalational agents i.e. isoflurane, sevoflurane and beta-blockers like esmolol have been used individually to decrease the blood loss in functional endoscopic sinus surgery (FESS)(711). Intravenous administration of Sodium nitroprusside (SNP), nitroglycerine (NTG), esmolol requires infusion pump or fixed drip rate which needs careful monitoring of blood pressure and pulse rate, vital parameters if neglected can lead to disastrous complications. But none of the single agent proved to be efficient as each of them had their own advantages and disadvantages.

Activation of fibrinolysis during and after surgery is a well-known phenomenon. Many mechanisms are associated with coagulation disorders, such as surgical trauma, blood loss and consumption of coagulation factors and platelets, using crystalloid and colloid during and after surgery, hypothermia, acidosis, foreign materials, etc. (12,13). In recent studies, systemic infusion of anti-fibrinolytic drugs have been used to reduce bleeding in various forms of surgery such as major orthopedic surgery, retro pubic prostatectomy, adeno-tonsillectomy, and endoscopic sinus surgery(1417).

Tranexamic acid is a synthetic antifibrinolytic agent that binds to lysine binding sites of plasmin and plasminogen. Saturation of binding sites cause separation of plasminogen from superficial fibrin and hence prevents fibrinolysis(18).

Any surgical procedure can cause considerable tissue damage and hence trigger the release of enzymes such as "tissue plasminogen activator" that converts plasminogen to plasmin and activates fibrinolysis process. Tranexamic acid prevents fibrinolysis by inhibiting the activity of this enzyme.

Systemic infusion of tranexamic acid is associated with several potential side effects such as nausea, diarrhea, allergic dermatitis, impaired vision, impaired color vision, and particularly thromboembolic events(19).

Intravenous tranexamic acid has been shown to be very useful in reducing blood loss in coronary artery bypass, spinal surgery, maxillo-facial surgery, orthotopic liver transplant, and total hip or knee arthroplasty(2022). Tranexamic acid has been used in adult tonsillectomy surgery in dose of 15 mg/kg(23). It has also been used for control of blood loss for functional endoscopic sinus surgery in children(24). Tranexamic acid also has been used topically for control of bleeding in functional endoscopic sinus surgery(24).

Ethamsylate is a synthetic hemostatic drug acting in first step of hemostasis by improving platelet adhesiveness and restoring capillary resistance. Recent studies showed that ethamsylate promotes p-selectin dependent platelet adhesiveness. It has also been associated with decreased concentrations of 6-oxoprostaglandin F1a, a stable metabolite of prostacyclin. Ethamsylate inhibits synthesis of 6-oxoprostoglandin F1 alpha, prostaglandin F2 alpha, prostaglandin E2, and thromboxane B2. Increasing the concentration of ethamsylate increases the inhibition of synthesis. It is suggested that ethamsylate has no anti-cyclooxygenase activity, but acts by inhibiting the activity of prostacyclin synthetase, endoperoxide reductase, endoperoxide isomerase, and thromboxane synthetase(25). Prostacyclin is a potent vasodilator and may be implicated in reperfusion. It is also a disaggregator of platelets.

Ethamsylate is indicated in cases of capillary bleeding. It inhibits biosynthesis and action of those prostaglandins which cause platelet disaggregation, vasodilatation and increased capillary permeability.

Well controlled trials clearly show the therapeutic efficacy of ethamsylate in dysfunctional uterine bleeding with the magnitude of blood loss directly proportional to severity of menorrhagia(26,27). Other well controlled trials showed therapeutic efficacy of ethamsylate in periventricular hemorrhage in very low birth weight babies(28) and surgical or postsurgical capillary bleeding. Oral route has been tried for control of epistaxis and also in dacryocystorhinostmy (DCR)(29).

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Hence, we decided to compare these two agents by intravenous route as bolus dose for reduction of blood loss and improvement of surgical field for functional endoscopic sinus surgery and study the merits and demerits respectively.

AIMS AND OBJECTIVES

1. To compare efficiency and safety of tranexamic acid and ethamsylate for functional endoscopic sinus surgery.
2. To study hemodynamic stability.
3. To study the effect on blood loss and quality of surgical field.
4. To notify side effects if any.

MATERIAL AND METHODS

Research plan

After approval of ethical committee and written informed consent from patients, 100 patients of age between 15-50 years, american society of anaesthesiologist grade I & II undergoing functional endoscopic sinus surgery in ear, nose and throat operation theatre were studied.

Group A = 50 Patients who received single BOLUS dose Tranexamic acid 10mg/kg in 100 cc normal saline over 10 minutes after induction.
Group B = 50 Patients who received single BOLUS dose Ethamsylate 10mg/kg in 100 cc normal saline over 10 minutes after induction.

These 100 patients were randomly divided into two groups by computerized randomization after following exclusion criteria. Equal numbers of cases of dacryocystorhinostmy surgery were added randomly to each of the group and odd numbered cases were excluded from study.

Tranexamic acid Injections were available with the department. Ethamsylate injection ampoules were purchased for the purpose of study.

Selection of cases (Inclusion & Exclusion Criteria)

Exclusion Criteria

1. Patients < 15 years of age
2. Patients preferring local anaesthesia for surgery
3. Patients with major systemic diseases like rheumatic heart disease, ischemic heart disease, hypertension, heart blocks, diabetes mellitus, anemia, sick sinus syndrome, sinus bradycardia.
4. Respiratory diseases like chronic obstructive pulmonary disease
5. Renal and hepatic derangements
6. Disease of central nervous system
7. Allergic fungal sinusitis
8. Revision surgery.
9. Patients on beta blockers, autonomic nervous system active drugs, agents influencing blood coagulation and long standing corticosteroids.
10. Patients with history of thromboembolic episodes.

Inclusion Criteria

1) Patients with chronic sinusitis resistant to medical treatment.
2) Computerized tomography paranasal sinus disease grade 1 & 2(30)
3) Patients with chronic sinusitis with multiple polyposis undergoing functional endoscopic sinus surgery
4) Patients of chronic dacryocystitis undergoing functional endoscopic sinus surgery.
5) American society of anaesthesiologist status I & II
6) Age group between 15 to 50 years
7) Sex – both males & females
8) Weight – 45 to 70 kg.
9) Elective functional endoscopic sinus surgery under general anaesthesia of duration 45 to 90 minutes

ANAESTHESIA TECHNIQUE

Premedication on Pre-operative day

On pre-operative night, tablet ranitidine 150 mg orally is given to all patients of both groups.

All pre-requisite consents and nil by mouth status were advised. Routine investigations were checked – hemoglobin, platelet count, bleeding time, clotting time, prothrombin time, blood sugar, blood urea level, serum electrolytes, serum creatinine, serum bilirubin, urine sugar and albumin. Whole Blood was advised to be kept ready. Peripheral intravenous access was established in all patients with wide bore cannula (16G or 18G).

Premedication before Induction

1. Injection glycopyrrolate 5 µg/kg intramuscularly 30 minutes before induction
2. Injection ranitidine 1 mg / kg intravenously
3. Injection ondensetron 0.08 mg/kg intravenously
4. Injection midazolam 0.03 mg/kg intravenously
5. Injection pentazocine 0.3mg/kg intravenously

The anesthetic technique was same for all patients of both groups and surgeon was blinded for the technique and drug used.

Monitors and Facilities available:

1. Electrocardiography with defibrillator
2. Pulse oximeter,
3. Respiratory gas monitor
4. Noninvasive blood pressure monitor
5. Temperature,
6. End tidal carbon dioxide monitor
7. Foleys catheter

Induction of general anaesthesia:

Inj. thiopentone sodium, 3-5 mg/kg intravenously Inj. succinylcholine 2 mg/kg intravenously

Intubation:

Appropriate sized cuffed portex endotracheal tube was passed orally.
Throat packing was done.

Maintenance:

Maintenance of general anaesthesia with O_2 33% and N_2O 66% with isoflurane 0.2%-0.8% with intermittent positive pressure ventilation on bain's circuit with vecuronium 0.08 mg/kg as skeletal muscle relaxant to keep end tidal CO_2 in the range of 32±2 mm Hg.

Intravenous fluids:

Ringer's lactate 2 ml/kg/ hour
Position: 15^0 Head up
Baseline:Pulse rate, systolic & diastolic blood pressure, mean arterial pressure, saturation of oxygen are noted.

Both groups received a topical application of 4% lignocaine on nasal mucus membranes for 10 minutes. After removal of pledges, infiltration of 2% lignocaine with adrenaline1in2lacs, submucosally was done into medial infundibular wall by surgeons.

After induction group A received single bolus dose of tranexamic acid 10mg/kg intravenously in 100 ml normal saline over 10 minutes, while patients of group B received single bolus dose of ethamsylate 10mg/kg intravenously in 100 ml normal saline over 10 minutes. Surgeon was blinded for the drug given to each patient.

Atropine 0.6 mg intravenously was given intravenously, if heart rate dropped to less than 60 beats/ minute.

Blood pressure, heart rate, SPO_2 & $ETCO_2$ were recorded at intervals of 10 minutes during periods of anaesthesia. Patient was considered as failed cases when other drugs were used to induce hypotension or if infusion of either of the drug is needed to control the blood loss.

Blood loss was calculated from suction bottles, by weighing the weight of dry & wet gauze pieces. Visual estimation of blood loss is done by moist 4X4 gauze piece, if mildly moist constituted 8 ml, moderately moist 10 ml, if completely soaked 12 ml[-(3133)]. Blood loss > 20% of estimated blood volume was be replaced by blood. Numbers of blood transfusions required were calculated for both the groups.

All operations were performed by the same surgeon. Quality of surgical field was judged by surgeon and classified as per Boezaart(7) et al:-

Grade	Description
0	no bleeding, cadaveric condition
I	slight bleeding; no suctioning of blood required
II	Slight bleeding; occasional suctioning required. Surgical field not threatened.
III	Slight bleeding; frequent suctioning required. Bleeding threatened surgical field a few seconds after suction removed.
IV	Moderate bleeding; frequent suctioning required. Bleeding threatened surgical field directly after suction was removed.
V	Severe bleeding; constant suctioning required. Bleeding appeared faster than could be removed by suction. Surgical field severely threatened and surgery not possible.

Surgeon was blinded to the medication used as well as to the monitor recording the hemodynamic variables. Beep on monitor was silenced.

If severe bradycardia or tachycardia not responding to treatment was noticed, then those patients were discarded from the study.

Vital parameters and surgical field assessment was done in both groups. Blood sample was sent for hematocrit, hemoglobin, platelet count, prothrombin time, bleeding time, clotting time fifteen minutes before end of the surgery. Spontaneous eye opening, Verbal response, orientation time was recorded. Side effects if any were noticed.

Total duration of surgery & anaesthesia noted.

Reversal & extubation:
Throat pack was removed before extubation.
Reversal done with,

Inj. glycopyrolate 10 µg / kg intravenously and
Inj. neostigmine 0.04 mg/ kg intravenously
Extubation was done after thorough suctioning in deep inspiration after cuff was deflated.

Postoperative Monitoring:
Monitoring was done in post anaesthesia care unit for 120 minutes. Vital parameters were monitored every 15 minutes for 2 hours in anaesthesia care unit. Sample was sent for hematocrit, hemoglobin, prothrombin time, bleeding time, clotting time and platelet count immediate postoperatively.

OBSERVATIONS AND RESULTS

Table 1. Genderwise distribution in group A and group B.

Gender	Group		Total	p-value
	Group A	Group B		
Male	28	21	49	0.230
Female	22	29	51	
Total	50	50	100	

Conclusion: - By using Chi-square test, p-value is > 0.05 therefore there is no significant difference between proportion of gender in group A and group B.

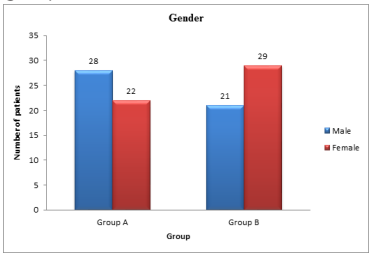

Figure 1

Table 2. Comparison of age in group A and group B.

Group	Number of patients	Age (years)		p-value
		Mean	SD	
Group A	50	36.28	9.37	0.889
Group B	50	36.02	9.29	

Conclusion: - By using 2 independent sample t-test, p-value is > 0.05 therefore there is `no significant difference between mean age (years) in group A and group B.

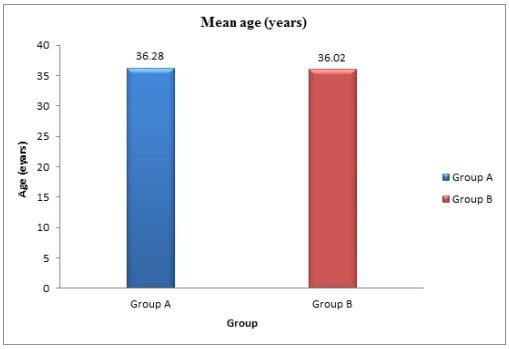

Figure 2

Table 3. Comparison of weight (Kg) in group A and group B.

Group	Number of patients	Weight (kg)	p-value	
		Mean	SD	
Group A	50	63.76	7.52	0.220
Group B	50	61.88	7.04	

Conclusion: - By using 2 independent sample t-test, p-value is > 0.05 therefore there is no significant difference between mean weight (kg) in group A and group B.

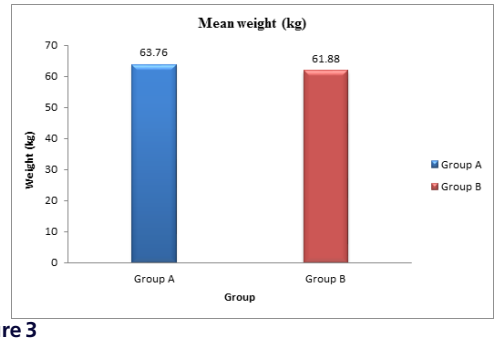

Figure 3

Table 4. Comparison of heart rate in group A and group B.

Heart rate at	Group A (n=50)		Group B (n=50)		p-value
	Mean	SD	Mean	SD	
0 min	84.92	6.63	86.60	5.77	0.179
10 min	85.90	6.64	87.28	5.56	0.263
20 min	86.52	5.85	88.24	4.94	0.116
30 min	87.08	4.87	88.42	4.66	0.163
40 min	87.38	5.04	88.45	4.70	0.278
50 min	87.78	4.51	88.20	4.93	0.656
60 min	88.36	4.55	89.24	4.35	0.325
70 min	88.60	4.50	89.74	4.21	0.194
80 min	88.66	4.37	89.54	3.48	0.269
90 min	89.14	4.14	90.30	3.90	0.152
Post op 15 min	87.72	4.89	87.56	4.78	0.869
30 min	88.04	5.07	86.64	5.26	0.178
45 min	87.84	5.30	86.70	5.53	0.295
60 min	87.42	5.65	85.76	4.93	0.121
75 min	88.28	5.20	87.62	4.71	0.508
90 min	88.32	4.98	88.20	4.74	0.902
105 min	88.82	4.39	88.72	3.77	0.903
120 min	88.74	3.45	89.26	4.11	0.495

*significant

Conclusion: - By using 2 independent sample t-test, p-value is > 0.05 therefore there is no significant difference between mean heart rate in group A and group B at 0 min to 120 min.

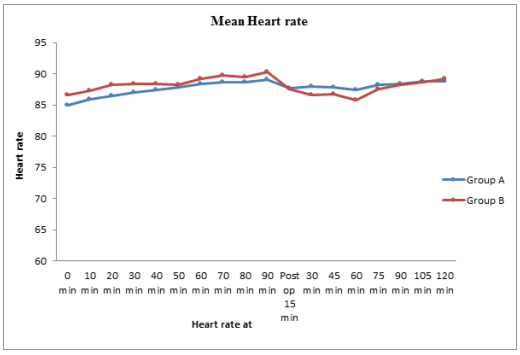

Figure 4

Table 5. Comparison of systolic blood pressure (SBP) in group A and group B.

SBP at	Group A (n=50)		Group B (n=50)		p-value
	Mean	SD	Mean	SD	
0 min	113.48	5.09	115.04	4.28	0.101
10 min	114.44	4.20	115.36	3.19	0.221
20 min	114.52	3.81	115.64	3.12	0.111
30 min	114.40	3.68	115.76	2.70	0.038*
40 min	114.76	4.31	115.76	3.42	0.202
50 min	115.24	4.33	115.00	4.49	0.786
60 min	115.20	4.20	114.36	4.67	0.347
70 min	115.08	3.39	114.96	3.39	0.860
80 min	114.36	4.60	115.48	3.23	0.162
90 min	115.44	4.12	116.16	3.63	0.356
Post op 15 min	115.56	4.39	114.60	4.52	0.284
30 min	115.52	3.78	114.88	3.64	0.391
45 min	116.08	3.28	115.08	4.02	0.177
60 min	115.32	2.87	114.52	3.52	0.216
75 min	115.80	4.15	114.88	4.02	0.263
90 min	115.60	3.61	115.24	4.71	0.669
105 min	115.44	3.31	114.76	4.57	0.396
120 min	116.08	2.97	115.08	3.46	0.124

*significant

Conclusion: - By using 2 independent sample t-test, p-value is > 0.05 therefore there is no significant difference between mean systolic blood pressure in group A and group B except 30 min.

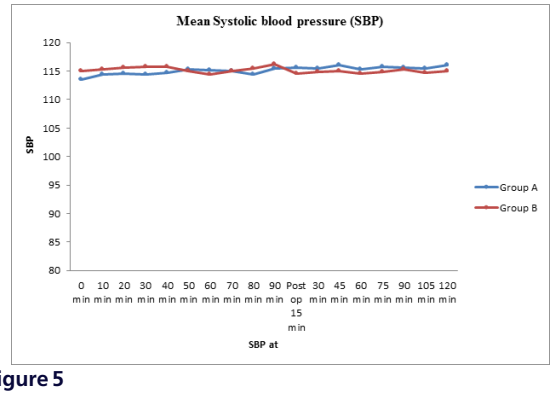

Figure 5

Table 6. Comparison of diastolic blood pressure (DBP) in group A and group B.

DBP at	Group A (n=50)		Group B (n=50)		p-value
	Mean	SD	Mean	SD	
0 min	80.70	4.76	80.44	4.50	0.780
10 min	81.16	4.32	80.84	4.35	0.713
20 min	81.40	4.24	80.94	4.13	0.584
30 min	82.00	3.81	81.92	3.75	0.916
40 min	82.32	4.19	82.04	4.25	0.741
50 min	81.56	5.00	81.80	4.32	0.798
60 min	81.48	4.55	82.44	4.30	0.281
70 min	81.92	4.76	82.24	4.44	0.729
80 min	81.84	4.44	82.44	4.59	0.508
90 min	81.40	4.43	81.12	4.28	0.749
Post op 15 min	81.80	4.09	81.68	4.79	0.893
30 min	81.52	3.56	81.60	4.14	0.918
45 min	81.26	3.75	81.72	3.93	0.551
60 min	81.96	3.39	82.44	3.24	0.471
75 min	81.68	3.82	82.32	4.28	0.432
90 min	82.00	4.30	82.32	4.23	0.708
105 min	82.12	3.67	82.72	3.97	0.435
120 min	82.28	3.90	82.52	3.85	0.757

Conclusion: - By using 2 independent sample t-test, p-value is > 0.05 therefore there is no significant difference between mean diastolic blood pressure (DBP) in group A and group B at Intra op 0 min and 90 min and Post op 15 min to 120 min.

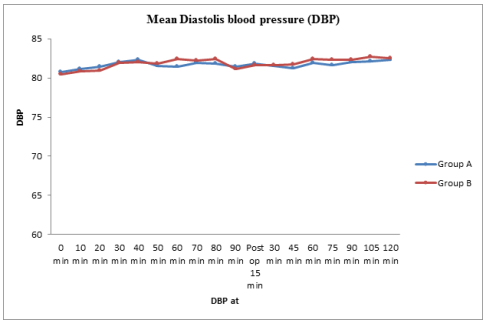

Table 6

Table 7. Comparison of mean arterial blood pressure (MAP) in group A and group B.

MAP at	Group A (n=50)		Group B (n=50)		p-value
	Mean	SD	Mean	SD	
0 min	91.63	3.79	91.97	3.40	0.631
10 min	92.25	3.49	92.35	3.14	0.889
20 min	92.44	3.46	92.51	3.03	0.919
30 min	92.80	3.03	93.20	2.75	0.491
40 min	93.13	3.33	93.28	3.25	0.824
50 min	92.79	3.63	92.87	3.23	0.908
60 min	92.72	3.68	93.08	3.26	0.606
70 min	92.97	3.70	93.15	3.29	0.805
80 min	92.68	3.86	93.45	3.39	0.290
90 min	92.75	3.33	92.80	3.27	0.936
Post op 15 min	93.05	3.38	92.65	3.46	0.560
30 min	92.85	2.86	92.69	2.94	0.783
45 min	92.87	2.73	92.84	2.90	0.962
60 min	93.08	2.60	93.13	2.24	0.913
75 min	93.05	3.06	93.17	3.08	0.845
90 min	93.20	3.16	93.29	2.96	0.879
105 min	93.23	2.81	93.40	2.98	0.765
120 min	93.55	2.79	93.37	2.90	0.761

Conclusion: -
By using 2 independent sample t-test, p-value is > 0.05 therefore there is no significant difference between mean mean arterial pressure (MAP) in group A and group B at Intra op 0 min and 90 min and Post op 15 min to 120 min.

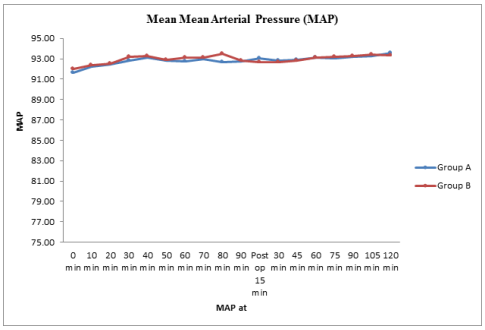

Table 7

Table 8. Comparison of blood loss (milliliters) in group A and group B.

Blood loss at	Group A (n=50)		Group B (n=50)		p-value
	Mean	SD	Mean	SD	
15 min	35.20	5.80	39.00	6.78	0.003
30 min	53.80	8.30	64.20	11.97	< 0.001
45 min	70.00	9.69	83.60	10.64	< 0.001
60 min	85.20	9.74	101.60	10.17	< 0.001
75 min	99.40	6.82	124.80	7.07	< 0.001
90 min	106.40	5.63	128.40	7.10	< 0.001

Conclusion: -
By using 2 independent sample t-test, p-value is > 0.05 therefore there is no significant difference between mean blood loss in group A and group B at 15 min and 90 min.

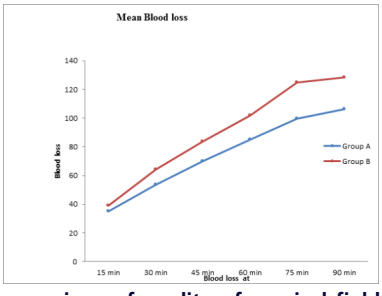

Table 8

Table 9. Comparison of quality of surgical field (Boezaart scale) in group A and group B.

B Scale at	Group A (n=50)			Group B (n=50)			p-value
	Min	Max	Median	Min	Max	Median	
15 min	0	0	0	1	1	1	< 0.001
30 min	1	3	2	1	4	2	< 0.001
45 min	1	3	2	1	3	2	0.010
60 min	1	3	2	1	4	2	0.023
75 min	1	3	1	1	4	2	< 0.001
90 min	1	2	1	1	4	2	0.001

Conclusion: - By using Mann-Whitney U test, p-value is < 0.05 therefore there is significant difference median Boezaart scale at 15 minutes to 90 minutes in group A and group B.

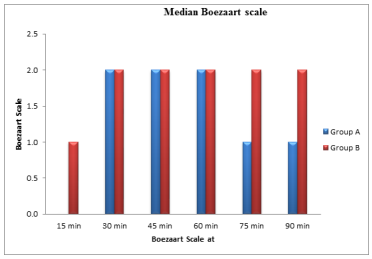

Table 9

SUMMARY AND CONCLUSION

This study was designed to study the effect of intravenous tranexamic acid and intravenous ethamsylate in functional endoscopic sinus surgery. The aims and objectives were to study the hemodynamic stability, quality of surgical field and side effects if any after intravenous administration of tranexamic acid and ethamsylate. This was a prospective, randomized study. In this study 100 patients of age group 15 to 50, belonging to ASA I or ASA II were randomized as per a computer-generated code.

The aims and objectives of our study were:

1. To compare efficiency of tranexamic acid and ethamsylate for functional endoscopic sinus surgery.
2. To study hemodynamic stability in functional endoscopic sinus surgery after intravenous administration of tranexamic acid and ethamsylate
3. To compare their effect on blood loss and quality of surgical field
4. To observe side effects, if any

Thus, from this study we can conclude that both these agents provide bloodless field without affecting the mean arterial pressure. Both these drugs do not affect the hemodynamic parameters perioperatively. Blood loss is clinically as well as statistically significant but with tranexamic acid the quality of surgical field is much superior than that of ethamsylate.

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