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The effect of local instillation of tranexamic acid on the gallbladder bed after laparoscopic cholecystectomy on the risk of postoperative bleeding in difficult cases: a randomized controlled study

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ABSTRACT

Introduction: Bleeding during laparoscopic cholecystectomy can occur from the gallbladder bed, especially if there is difficulty during the dissection due to acute inflammation. The bleeding is usually minor from the small arteries running between the gall bladder and its bed. Tranexamic acid (TXA) is a drug that used topical and parenteral to decrease the bleeding during cardiac and spine, and trauma surgeries. It has antifibrinolytic effect by inhibiting degradation of blood clot and also probably degradation of platelet aggregation. We hypothesized that the local instillation of TXA in the gall bladder bed after laparoscopic cholecystectomy can decrease the bleeding in the form of decrease in the haematocrit and haemoglobin levels in the drain after surgery.

Objective: to evaluate the efficacy of local instillation of TXA in the gallbladder bed in reducing postoperative bleeding following difficult laparoscopic cholecystectomy.

Methods: This randomized double-blinded clinical study involved 80 adult patients treated at our university institution from December 2021 to January 2024. The patients were categorized into two groups. Group A consisted of 40 patients who, after achieving meticulous hemostasis of the bleeding points in the liver bed, received 500 mg of TXA dissolved in 20 ml of normal saline locally in the liver bed. Group B, also comprising 40 patients, underwent the same hemostatic procedure until no significant bleeding was observed, followed by the instillation of 20 ml of normal saline in the gall bladder bed. In both groups, the drain was occluded for one hour. Drain output was measured, and the haematocrit and haemoglobin levels of the drain fluid were evaluated at 6 hours and 24 hours. The haemoglobin level was compared to preoperative levels. Postoperative complications were documented.

Results: 80 patients were eligible and after excluding 20 patients that were easy dissection of the gallbladder without potential risk of bleeding, so sixty patients were the scope of the study and divided into two groups. No serious bleeding was observed in any case, and hemoglobin and hematocrit levels in the drain were assessed at 6 and 24 hours' post-procedure. In the TXA group, there was significant decrease in the 6h hematocrit concentration in the drain from 7.59±3.09 % to 5.76±2.88 % (P= 0.0213), and also hemoglobin decreased in the drain from 2.29±1.48 gm/dl to 11.21± 1.09 gm/dl (P=0.002), but these differences were not significant after 24 hours. Additionally, there was statistically insignificant difference between the two groups regarding the preoperative and 6 hours' postoperative hemoglobin concentration in blood (P=0.521 and 0.710, respectively).

Conclusion: The local administration of Tranexamic acid in the gallbladder bed following dissection may serve as an effective method to enhance hemostasis in the operative field, improve laparoscopic visibility, and reduce the likelihood of conversion to open surgery.

KEYWORDS: Tranexamic acid; laparoscopic cholecystectomy; postoperative bleeding; topical hemostasis; randomized controlled trial; gallbladder bed.

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INTRODUCTION

Laparoscopic cholecystectomy had been established as the mainstay for the treatment of symptomatic cholelithiasis (1). Several literatures reports focused on the potential complications of this procedure, meanwhile few studies discussed possible bleeding probability and possible prophylaxis (2). During laparoscopic cholecystectomy, bleeding can occur occasionally from the gall bladder bed especially if there is difficult dissection due to acute inflammation. Bleeding is usually minor from small arteries running between the gall bladder and its bed and less often major bleeding can occur from the middle hepatic vein that must be controlled surgically (3).

Tranexamic acid (TXA) is a well-known drug since 1970 that had been recently used to decrease the bleeding in cardiac and spine surgeries (3,4). Its hemostatic effect works on lysine binding sites by competing plasminogen, plasmin, and tissue plasminogen activator, so its antifibrinolytic effect acts by inhibiting the degradation of blood clots and also probable degradation

of platelet aggregation (5). TXA has a half-life of 80 minutes and its effect can prolong to up to 17 hours. It can be used both parenteral and topical in some surgeries as spine and trauma surgery (6,7,8). It can be applied topically by local instillation as injecting it intrauterine by hysteroscopy beside its common systemic use. There are also available literatures that focused on its systemic use for possible prophylaxis against bleeding in laparoscopic cholecystectomy without noticing significant results (9). We postulated that local application of TXA (0.5 gm in 20 ml solution) in the gall bladder bed during laparoscopic cholecystectomy might reduce bleeding from the bed by lowering the hemoglobin and hematocrit levels in the drain following the procedure. The purpose of this research was to assess the effectiveness of topical TXA application on the gallbladder bed as a preventative measure against bleeding in situations of difficult dissection because of thick adhesions and acute inflammation. Additionally, we sought to assess its impact on reducing hospital stays, morbidity, and early return to regular job activities. The hemoglobin and hematocrit levels in the drain six hours after surgery were the main outcome, while the duration of hospital stay and the hemoglobin level in the drain following surgery were the secondary outcomes.

PATIENTS AND METHODS

Study design

From December 2021 to January 2024, 80 adult patients receiving care at Tanta University's General Surgery Department participated in this prospective randomized double-blind clinical trial. The research comprised adult patients between the ages of 21 and 60 who had laparoscopic cholecystectomy procedures with challenging intraoperative dissection because of adhesions or acute inflammations. Informed written permission was acquired from the patients, and we received clearance from our institution's ethical committee board. The participants and the ethics committee were quickly informed of any unforeseen dangers that emerged throughout the process, and the necessary measures were put in place. Patients with coagulation problems, bleeding disorders, anticoagulant use, or refusal to participate in the trial were not allowed to join. Furthermore, patients without considerable intraoperative bleeding or straightforward procedures that did not include the placement of a drain were not included.

Preoperative workup

Using the slip technique, 80 patients with symptomatic cholelithiasis who had laparoscopic cholecystectomy were randomly assigned to one of two groups. Every patient had a comprehensive clinical examination and a complete history of medication use, including anticoagulants and antiplatelets. Complete blood count (CBC), C-reactive protein (CRP), fasting blood sugar, renal function tests, and abdominal ultrasonography were among the laboratory tests carried out. In the prone position, peripheral blood samples were drawn from the patient's antecubital vein and put into two tubes: one for EDTA and the other for serum containing clot activator. After that, the serum tube was centrifuged for 15 minutes at 3000 g. An electronic automated analyzer (ERMA Inc. Poland, catalogue number 3459.9020) was used to produce a complete blood count (CBC), and a KONELAB PRIME 60i device was used to test CRP and fasting blood sugar using kits from Thermo Fisher Scientific Oy-Finland (catalogue numbers 981933, 981304, and 981820, respectively).

Operative procedure

A typical 4-port laparoscopic cholecystectomy was carried out after the administration of general anesthesia. Following meticulous hemostasis of the liver bed's bleeding points, 40 patients in group A received 500 mg of TXA dissolved in 20 ml of normal saline locally through the liver bed's right port. A piece of gauze was then introduced to hold the medication in place for approximately three minutes, after which it was removed, a drain was inserted, and the procedure was closed for an hour. Similar to group A, group B (40 patients) had the same operation, which included conventional hemostasis care until there was no more noticeable bleeding, followed by the instillation of 20 milliliters of normal saline in the gallbladder bed, the insertion of a drain, and its closure for one hour. The case was eliminated from the research in both groups if it was a straightforward procedure with no adhesions and very little chance of bleeding.

Post-operative care

Following surgery, blood pressure and heart rate were monitored every six hours. All patients were monitored until their release, drain output was noted, and drain fluid haematocrit and hemoglobin were examined after six and twenty-four hours. If fewer than 50 cc were seen over the course of 24 hours, the drain was removed. After six hours, the Hb level was taken and compared to the preoperative values. Any potential morbidity was recorded, including nausea, vomiting, diarrhea, and significant postoperative pain (an increase in the pain score of greater than 3). Additionally, the duration of the hospital stay was noted and documented.

Statistical analysis

In a pilot study, 10 patients (not included in the final study) who were scheduled for laparoscopic cholecystectomy were randomly assigned to one of two groups: group A (5 patients) received 500 mg of tranexamic acid in 20 ml solution on the gall bladder bed following the procedure, and group B (5 patients) received normal saline on the gall bladder bed following the procedure. The postoperative 6-hour hematocrit level in the drain dropped from 9.580± 2.388% to 4.460± 3.112% after local TXA instillation ($P = 0.019$). In order to detect a significant difference in the postoperative 6-hour hematocrit level in the drain of 3% at an alpha value of 0.05 and 95% power of the study, 29 patients were needed in each group, according to the sample size calculation. In order to account for the likelihood of dropout cases (easy-going instances that didn't need drain implantation), forty patients were included in each group. The data was statistically analyzed using the SPSS computer software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine if the data was normal. The Chi-square test was used to examine categorical data, which were then shown as numbers and frequencies. The unpaired t-test was used to assess the parametric data, and the mean and standard deviation were the results. When p was less than 0.05, the significant value was taken into account.

RESULTS

Ninety-one patients undergoing laparoscopic cholecystectomy were assessed for eligibility for this randomized clinical trial, 80 patients of them were randomly distributed into the two groups after 11 patients were excluded (6 of them did not meet the inclusion criteria of the study and 5 patients refused to participate in the study). In each group,10 patients did not receive the allocated intervention as there were no adhesions in the gall bladder and the manoeuvre was such easy that there was no need to insert a drain, the other 30 patients received the allocated interventions, and their data were collected and analyzed successfully. Fig 1

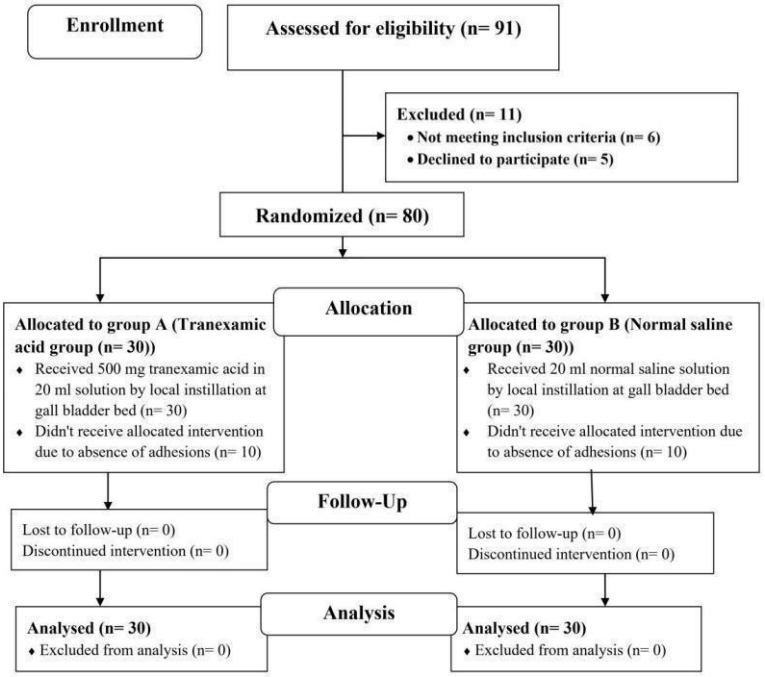

Figure 1. Flow diagram illustrating the enrollment, randomization, allocation, follow-up, and analysis of study participants.

The basic demographic data of the studied patients were comparable between the two studied groups as regards age, body mass index, gender, and the duration of surgery (p = 0.918, 0.518, 0.789, and 0.961 respectively). Moreover, the presence of co-morbidities as diabetes mellitus, hypertension, and ischemic heart disease was insignificant between the two groups (P = 0.733, 0.774, and 0.746 respectively). Table 1

The use of local instillation of tranexamic acid in the gall bladder bed after removal of the bladder significantly decreased the 6 h hematocrit concentration in the drain from 7.59±3.09 % to 5.76±2.88 % (P = 0.0213) and decreased the 6 h hemoglobin concentration in the drain from 2.29±1.48 gm/dl to 11.21± 1.09 gm/dl (P = 0.002). However, the 24 h hematocrit and hemoglobin concentrations in the drain were comparable between the two groups (P = 0.688 and 0.241). Table 2

There was a statistically insignificant difference between the two groups as regards the preoperative and 6 hours' postoperative hemoglobin concentration (P = 0.521 and 0.710 respectively). Furthermore, comparison of 6 hours' hemoglobin concentration to the preoperative values showed an insignificant difference in both groups (P = 0.307 and 0.212 respectively). Table 3

The length of hospital stays was insignificant between the two studied groups (P = 0.328). Moreover, the incidence of postoperative complications such as severe postoperative pain, nausea and vomiting, and diarrhea was statistically insignificant between the two groups (P = 0.729, 0.774, and 0.704 respectively). No reported cases of postoperative bleeding in the two studied groups. Table 4

Table 1: Demographic data of the studied patients

		Group A	Group B	P value	CI (95%)
Age (Years)		49.67± 14.06	50.03± 13.47	0.918	-6.751; 7.485
BMI (kg/m²)		31.07± 4.24	31.77± 4.11	0.518	- -1.458; 2.858
Gender	M	10 (33.33%)	12 (40.00%)	0.789	

	F	20 (66.57%)	18 (60.00%)		
Co-morbidities	D.M	8 (26.67%)	10 (33.33%)	0.733	
	Hypertension	9 (30.00%)	8 (26.67%)	0.774	
	IHD	5 (16.67%)	7 (23.33%)	0.746	
Duration of the surgery (min)		65.18± 23.91	65.50± 28.11	0.961	-13.153; 13.819

Data were presented as mean ± standard deviation or as number and percent. Group A (Tranexamic acid group (30 patients)) Group B (Normal saline group (30 patients)) CI; Confidence interval: D.M; Diabetes Mellitus: IHD; Ischemic Heart Disease

Table 2: The postoperative hemoglobin and hematocrit concentration in the drains.

	Group A	Group B	P value	CI (95%)
6 h haematocrit concentration (%)	5.76±2.88	7.59±3.09	0.021*	0.2841; 3.369
6 h haemoglobin concentration (gm/dl)	1.21± 1.09	2.29±1.48	0.002*	0.4107; 1.756
24 h haematocrit concentration (%)	2.91±1.45	3.07± 1.61	0.688	-0.632; 0.952
24 h haemoglobin concentration (gm/dl)	0.50±0.45	0.66±0.57	0.241	-0.107; 0.421

Data were presented as mean ± standard deviation, Group A (Tranexamic acid group (30 patients)) Group B (Normal saline group (30 patients)) *Denotes significant changes

Table 3: The preoperative and postoperative hemoglobin concentration.

	Group A	Group B	P value	CI (95%)
Preoperative haemoglobin level (gm/dl)	11.87±1.08	12.06±1.16	0.521	-0.392; 0.765
6 h postoperative haemoglobin level (gm/dl)	11.58± 1.10	11.69±1.12	0.710	-0.465; 0.679

Data were presented as mean ± standard deviation. Group A (Tranexamic acid group (30 patients)) Group B (Normal saline group (30 patients))

Table 4: The length of hospital stays and incidence of postoperative complications.

		Group A	Group B	P value	CI (95%)
Length of Hospital stay		13.07±6.41	14.70±6.44	0.328	-1.687; 4.954
Incidence of complications	**Severe postoperative pain**	6 (20.00%)	4 (13.33%)	0.729	
	Nausea and vomiting	9 (33.33%)	8 (27.78%)	0.774	
	Diarrhea	3 (10.00%)	5 (16.67%)	0.704	
	Postoperative bleeding	0 (0.00%)	0 (0.00%)	-	

Data were presented as mean ± standard deviation or as number and percent. Group A (Tranexamic acid group (30 patients)) Group B (Normal saline group (30 patients)

DISCUSSION

During laparoscopic cholecystectomy, hemorrhage from the gallbladder bed can increase morbidity and mortality and be a risk factor for conversion to laparotomy. If the middle hepatic vein or one of its branches is injured, the bleeding should be surgically controlled; if not, diathermy and sealing devices can be used to control the bleeding (3).

A well-known medication for reducing bleeding after surgery and trauma, tranexamic acid (TXA) works by blocking plasminogen activity and fibrinolysis, which promotes clot formation and reduces capillary leaking and blood loss without changing the patient's coagulation profile. (10)

TXA has been used systemically to reduce blood loss during laparoscopic surgery. In one study, 60 patients undergoing laparoscopic cholecystectomy were split into two groups. One group received a bolus dose of 20 mg/kg TXA at the onset of anesthesia. The study group that received tranexamic acid experienced less blood loss than the control group that did not receive TXA, but this difference was not statistically significant (9).

Preoperative and postoperative hemoglobin variations were less than 1 mg/dl in 23 out of 25 individuals who received two intravenous TXA doses in a trial including 50 patients who had laparoscopic sleeve gastrectomy. In contrast, 18 out of 25 patients in the control group had hemoglobin variations more than 1 mg/d before and after surgery (11).

In fact, there have been successful topical application studies of TXA in several operations. After performing spine procedures and closing the drain for one hour, Liang JG et al. reported their experience with topical retrograde injection of TXA via the drain. They said that TXA successfully decreased postoperative blood loss and postoperative hospital stay (7). They characterized this approach as straightforward, manageable, and appropriate for both patients and surgeons. In comparison to the control group, the TXA group saw decreased postoperative total blood loss and total drainage (1027.14 ± 466.56 vs 1390.07 ± 314.85 mL, P = 0.006; 322.20 ± 187.32 vs 605.50 ± 184.70 mL, P = 0.000, respectively). The TXA group's mean hemoglobin and hematocrit levels at discharge were considerably higher than those of the control group (11.77 ± 1.78 g/dL vs. 10.67 ± 0.94 g/dL, P = 0.002; 34.82 ± 3.57% vs. 31.79 ± 3.85%, P = 0.014).

Eighty patients were eligible for our study; twenty patients were excluded because their gallbladder dissection was simple and did not pose a risk of bleeding. This left sixty patients in the study's scope, who were split into two groups: group A received TXA locally in the gallbladder bed following dissection and standard hemostasis, while group B received only normal saline. After six and twenty-four hours, the hemoglobin and hematocrite levels in the drain were assessed, and there was no significant bleeding in any of the instances.Hemoglobin dropped from 2.29±1.48 gm/dl to 11.21±1.09 gm/dl (P = 0.002) and the 6-hour hematocrit concentration in the drain reduced from 7.59±3.09% to 5.76±2.88% (P = 0.0213) in the TXA group, but these changes were not significant after 24 hours. Additionally, there was no statistically significant difference between the two groups' blood hemoglobin concentrations before and six hours after surgery (P = 0.521 and 0.710, respectively).

To the best of our knowledge, our intervention is unique because we haven't found any comparable studies regarding the impact of TXA on the gallbladder bed. However, topical application of TXA has been thoroughly studied in various studies for the treatment of epistaxis (12), intra-articular injection in orthopedic surgeries (13,14), and intra-uterine injection following myomectomy (8). In this study, which involved 80 patients who had undergone myomectomy, participants were randomly assigned to receive either 1 g of TXA for every 1000 mL of the distention medium (intervention group) or 10 mL of a placebo (10 mL of 1.5% glycine) inside every 1000 mL of the distention medium. In addition to recording the surgeon's assessment of intraoperative bleeding, the quality of the operational view, and the length of the procedure, the objective was to document the change in hemoglobin levels 24 hours postoperatively in comparison to preoperative values.The TXA group's hemoglobin level was 1.11 ±.58 g/dL, whereas the placebo group's was 1.46 ± 0.61 g/dL (p =.015). The TXA group had a higher quality hysteroscopic view (p =.001), with 23 (60.5%) of the TXA group's cases having an excellent operative view compared to 8 (20.5%) of the placebo group's. The decrease of bleeding and the quality of the endoscopic image, which led to a superior surgical field and improved overall outcomes, were also positive outcomes.

The effectiveness of intravenous versus topical administration of TXA in patients undergoing primary total knee arthroplasty was compared in a meta-analysis that included 10 studies. The topical TXA group experienced 51.4 mL greater total blood loss (95 % CI -208.16 to 105.31 mL; n.s.), 52.1 mL greater estimated blood loss (95 % CI -155.27 to 51.03 mL; n.s.), and 52.3 mL less blood loss via drainage (95 % CI -50.74 to 185.66 mL; n.s.). However, there were no significant differences in the transfusion requirement, postoperative complications, blood loss, or change in hemoglobin levels between the topical and IV administration of TXA (14).

Clinical Implications

The study provides valuable evidence supporting the use of locally instilled tranexamic acid (TXA) in the gallbladder bed following laparoscopic cholecystectomy, especially in cases with difficult dissections due to acute inflammation or adhesions. Clinically, the significant reduction in hemoglobin and hematocrit levels in the drain fluid at 6 hours postoperatively suggests an early hemostatic benefit, which can translate into enhanced intraoperative visibility and reduced need for conversion to open surgery. Although no cases of major postoperative bleeding occurred in either group, the early drainage profile indicates that TXA may help minimize microvascular oozing, contributing to better immediate postoperative outcomes. This technique could become a valuable adjunct in enhancing the safety and efficiency of laparoscopic cholecystectomy, particularly in high-risk bleeding situations.

Strength Points

One of the primary strengths of this study is its double-blinded, randomized controlled design, which enhances the validity and reliability of the results. Another strength lies in the clear inclusion criteria, focusing specifically on patients with difficult dissections, thus targeting the subgroup most likely to benefit from hemostatic interventions. Moreover, the study used objective outcome measures (drain hemoglobin and hematocrit levels) at two time intervals (6 and 24 hours), which provided insight into the time-limited efficacy of topical TXA. Additionally, the inclusion of a control group receiving placebo (normal saline) strengthens the ability to attribute the differences observed to the intervention itself.

Limitations

Despite its strengths, the study has several limitations. Firstly, the sample size (60 patients after exclusions) limits the generalizability of the findings, especially for rare adverse events. Secondly, while early (6-hour) bleeding reduction was observed, the lack of significant difference at 24 hours raises questions about the duration of the effect of topical TXA. Third, the study did not evaluate long-term outcomes such as delayed bleeding, wound healing, or liver bed fibrosis. Moreover, only topical application of TXA was studied; comparison with intravenous or combined approaches was not explored. Lastly, since no patients experienced significant bleeding requiring transfusion or reoperation, the clinical significance of the observed biochemical changes remains to be fully elucidated.

CONCLUSION

The local instillation of 500 mg tranexamic acid into the gallbladder bed after difficult laparoscopic cholecystectomy appears to reduce early postoperative bleeding, as evidenced by decreased hemoglobin and hematocrit levels in drain fluid at 6 hours. This technique may offer a simple, safe, and cost-effective adjunct to standard hemostatic measures, potentially improving operative field clarity and decreasing the risk of intraoperative complications. However, these effects were not sustained at 24 hours, and no major bleeding or clinical deterioration was reported in either group, suggesting that while the intervention is helpful, its impact may be modest and short-lived.

Based on the findings of this randomized controlled study, local instillation of tranexamic acid (TXA) in the gallbladder bed is recommended during laparoscopic cholecystectomy in cases with difficult dissection to reduce early postoperative bleeding. While effective in the short term, larger studies are needed to evaluate long-term outcomes, compare topical versus systemic use, and standardize the protocol for broader clinical application.

List of Abbreviations

- **TXA**: Tranexamic Acid
- **CBC**: Complete Blood Count
- **CRP**: C-reactive Protein
- **BMI**: Body Mass Index
- **D.M**: Diabetes Mellitus
- **IHD**: Ischemic Heart Disease
- **SPSS**: Statistical Package for the Social Sciences
- **EDTA**: Ethylenediaminetetraacetic Acid

Ethical Considerations

This study was conducted following the Declaration of Helsinki and approved by the Ethical Committee of the Faculty of Medicine, Tanta University, Egypt (Approval Code: **35049-11-21**, IRB: **IRB0010038**, FWA: **FWA00022834**). All participants gave informed written consent before enrollment. Participants were informed about the objectives, procedures, potential risks, and their right to withdraw at any point without consequence. There were no anticipated risks beyond those typically associated with laparoscopic cholecystectomy.

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Author Contributions

- **Ahmed Amer**: Conceptualization, study design, surgery, and final manuscript approval
- **Sameh Ahmed**: Patient recruitment, operative intervention, and manuscript editing
- **Gamal I. Moussa**: Preoperative evaluation, data management, and interpretation
- **Elghamry E. Elghamry**: Methodology supervision, statistical support, and validation
- **Ahmed Swelam**: Intraoperative assistance, outcome assessment, and patient follow-up
- **Sherif Elgarf**: Manuscript review, critical revision, and ethical compliance assurance

All authors have read and approved the final manuscript.

Conflicts of Interest

The authors declare that there are **no conflicts of interest** related to this study, whether financial, professional, or personal.

Confidentiality of Data

All patient-related data collected during the course of this study were anonymized and stored securely. Access was limited to the research team only. Personal identifiers were not used in any publication, and privacy was maintained throughout the study period and beyond.

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