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RESEARCH ARTICLE
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SAFETY AND EFFECTIVENESS OF TOPICAL VERSUS SYSTEMIC ADMINISTRATION OF TRANEXAMIC ACID DURING CS IN A TERTIARY CARE HOSPITAL OF NORTHERN PAKISTAN

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ABSTRACT

INTRODUCTION: One of the most often carried out surgical operations globally is a caesarean section (CS.). Between 20-30 percent of all deliveries are thought to be managed by CS. Particularly in low- and middle-income nations like Pakistan, globally CS rates are increasing daily. Furthermore, at risk are blood transfusion related complications, delayed wound healing and extended hospital stays. Tranexamic acid enhances surgical hemostasis and helps to stop bleeding.

OBJECTIVE: To compare the effectiveness and safety of topical versus systemic administration of tranexamic acid (TXA) in reducing the intraoperative blood loss during CS.

MATERIAL AND METHODS: From January 2022 to November 2022, the Department of Gynecology & Obstetrics, District Head Quarter Hospital, Rawalpindi, carried out this comparative interventional study. From the labor room, 120 pregnant female receiving simple CS were chosen for this study. Every enrolled patient underwent an obstetric review and a thorough history. Among all the patients, either they kept in Group A (Topical TXA Group) or Group B (Systemic TXA Group). Using a sensitive weighing scale (up to 0.01g accuracy), intraoperative blood loss was calculated at the end of the surgery from all the abdominal sponges used during surgery by standardized gravimetric method i.e. all the gauzes, abdominal sponges and drapes soaked with blood was weighed, so documenting the total blood loss recorded. Suction bottle blood was recorded.

RESULTS: Average age of patients was 28.0+4.74 years, whereas average amount of blood loss among both the groups was 227.55+18.12 vs 262.38+17.86 which was statistically significant (p-value 0.000). Side effects included nausea, vomiting, hypotension and hypertension were also assessed and it was observed that there were statistically significant (*p*-value 0.000) difference in topical TXA versus systemic TXA pertaining to hypotension (1.7% vs 26.7%), hypertension (3.3% vs 31.7%), nausea (5% vs 6.7%) and vomiting (5% vs 18.3%).

CONCLUSION: The study concluded that topical TXA is both rapid and effective. The incorporation of topical TXA in routine practice may reduce blood loss and minimize the need for surgical interventions to control bleeding. Therefore, enhancing maternal health outcomes through the optimization of TXA utilization in CS.

KEYWORDS: cesarean, topical, systemic, intraoperative

INTRODUCTION

Caesarean section (CS) ranks among the most frequently conducted surgical procedures globally.[i] Approximately 20-30% of all deliveries are conducted via cesarean section. The global prevalence of CS is increasing daily, with a rate of 22% reported in Pakistan according to the Health Survey of 2017-2018. [ii] Although CS is a safe and effective procedure, it is not devoid of risks. Bleeding is one of the most significant risks associated with CS. Bleeding may originate from the incision site, as well as from vessels such as the epigastric, hypogastric, peritoneal, and uterine vessels (particularly along uterine angles), and branches of the internal iliac. Additionally, bleeding can occur from the site of placental separation in the uterus. If not controlled promptly, this bleeding can result in hypovolemic shock and acute renal shutdown. [iii,iv] The process of securing hemostasis carries a risk of injuries to adjacent organs, such as potential gut injury during ligation and bladder injuries resulting from diathermy. Additionally, there exists a risk of complications associated with blood transfusions, as well as delayed wound healing and extended hospital stays. Various studies indicate that the average blood loss during cesarean section is between 500 and 592 ml. [v,vi]

In managing intraoperative bleeding, meticulous surgical technique is essential. Surgeons should prioritize controlling the bleeding with clips, sutures, or electrocautery before resorting to hemostatic agents. [vii,viii] Topical hemostatic agents are employed in situations where electrocautery and sutures are not suitable, or when bleeding is diffuse. In certain situations, biologically active agents such as topical thrombin and fibrin sealants may be utilized; however, they are not accessible in Pakistan. Topical hemostatic agents exhibit unique mechanisms of action; however, they are not considered safe or optimal for managing bleeding areas due to the risk of damaging adjacent structures and organs. [ix,x]

Tranexamic acid (TXA) serves as an alternative method for managing hemorrhage. This synthetic antifibrinolytic agent is a competitive analogue of lysine that reversibly binds to lysine receptor sites in plasminogen. This binding displaces plasminogen from the fibrin clot and inhibits the proteolytic activity of plasmin; however, it is associated with an uncertain risk of thromboembolic events. It mitigates low pressure and low velocity blood loss, thereby preventing hemorrhage from venous channels. [xi,xii] The intravenous administration of TXA can reduce bleeding during surgery; however, due to the potential for thromboembolic events associated with this route, topical TXA has also been investigated. It demonstrates significant outcomes across various surgical procedures by utilizing an antifibrinolytic agent that effectively reduces blood loss and the need for transfusions in multiple surgical contexts, including cesarean sections. [xiii] TXA reduces bleeding and enhances surgical hemostasis. The systemic administration of TXA has been associated with side effects such as thromboembolism and seizures, whereas topical application of TXA has demonstrated minimal side effects due to its localized absorption and reduced systemic uptake. The topical application of TXA has been investigated in cardiac surgery, otolaryngology, and knee arthroplasty, utilizing various dosages; however, its use in obstetric patients is still limited. [xiv,xv,xvi,xvii]

A substantial amount of evidence supports the topical application of TXA in cesarean sections to decrease blood loss and the need for transfusions. There is a lack of literature concerning the role of Topical TXA. This study's findings will enhance the current understanding of the topical application of TXA in CS. This approach will assist patients in avoiding significant surgical interventions and related morbidity, while also alleviating the economic burden on both patients and hospitals regarding the necessity for blood transfusions and multiple medications to manage bleeding. Topical TXA can be routinely utilized in hospitals with limited resources. This approach minimizes operating time by decreasing blood loss and reducing the need for surgical interventions to control bleeding. This research seeks to enhance maternal health outcomes through the optimization of TXA use in cesarean sections.

MATERIALS AND METHODS

This comparative interventional study was conducted at the Department of Gynecology and Obstetrics, District Head Quarter Hospital, Rawalpindi, from January 2022 to November 2022, following formal approval from the hospital's ethical review board. This study selected all pregnant females undergoing uncomplicated cesarean sections from the labor room, following the acquisition of informed consent from all participants. Patients with known allergies or sensitivities to TXA, those with coagulation disorders or on anticoagulant therapy, individuals with comorbid conditions (including heart, kidney, or liver disease), pregnant females

experiencing vascular injury during uncomplicated cesarean sections, patients unresponsive to local and injectable TXA, those requiring hysterectomy and devascularization, individuals developing postpartum hemorrhage, and patients presenting for emergency cesarean sections were excluded from the study. A thorough history and obstetrical examination were performed for all enrolled patients. Sample size was calculated by using the WHO calculator taking 5% significance level, 80% power of the test, pooled standard deviation as 8.03[xviii], anticipated population mean as 746.04, test value of the population mean as 691.46. Sample size comes out as 120 patients. All patients were divided into two equal groups (60 patients in each group). Baseline laboratory investigations were conducted, including complete blood count, prothrombin time/activated partial thromboplastin time, liver function tests, and serum creatinine levels. In the Topical TXA Group, following the delivery of the baby and placenta, the surgeon initially achieved hemostasis by applying clamps on either side of the uterine incision. The placenta was then completely removed, along with any retained products of conception. An abdominal sponge measuring 24×24 cm and weighing 17 g was utilized. The incision site was treated with 2 grams of TXA, diluted in 100 ml of 0.9% sodium chloride, for a duration of 5 minutes before removal. The surgeon proceeded to close the initial layer of the uterus following standard technique and repaired the incision, subsequently mopping with an abdominal sponge. All active bleeding and potential bleeding sites were secured, and the remainder of the surgery was conducted according to standard procedures. Upon completion of the surgery, the surgeon conducted a count of all abdominal sponges utilized and recorded the intraoperative blood loss through a standardized gravimetric method. This involved weighing all gauzes, abdominal sponges, and drapes that were blood-soaked, employing a sensitive scale with an accuracy of 0.01g, and subsequently documenting the total blood loss. The collection of blood in the suction bottle was recorded. Intra operative blood loss was calculated by formula:

Weight of 1 abdominal sponge (24×24) = 17g; Weight of all sponges used =17× No. of sponges used (x); Weight in grams of soaked abdominal sponge after surgery = (y) The amount of blood loss (in gm) = (x-y); Since,1gm blood soaked equal to1ml of blood loss [xix] Total intraoperative blood loss (ml) = i.e. Blood volume in suction bottle + blood loss calculated from soaked abdominal sponges by above formula

On the other hand, systemic TXA Group given infusion containing 1g (10ml) TXA (Inj. Tramic, 5ml, of 500mg, manufactured by Ameeron Pharmaceuticals) diluted with 20ml of 5% glucose administered intravenously over a 5-minute period at least 10 minutes prior to skin incision and after spinal anesthesia. Rest of the surgery was done as per conventional method. Post operative care was provided as half hourly observation of heart rate, blood pressure and one hourly monitoring of urine output, oxygen saturation and fundal height. Any complications during hospital stay were noted. Complete blood picture (Blood CP) was done 6 hours postoperatively. Effectiveness of either treatment group will be assessed in terms of mean blood loss while safety was determined in terms of adverse effects such as nausea, vomiting, hypertension and hypotension. SPSS 26.0 software was utilized to enter and analyze the collected data. Quantitative variables were represented in terms of Mean (± S.D.) while, qualitative variables were reported in terms of frequencies (percentages). Independent sample *t*-test was applied to see the difference in mean blood loss among both study arms while, chi-square test was applied to see the difference in adverse outcomes (safety). *p*-value ≤0.05 considered statistically significant.

RESULTS

Average maternal age of the study subjects was 28.0+4.74 years, with minimum 20 and maximum 40 years. Average gravida in the study among both the groups was 3.15+1.53 in group A vs 3.41+1.29 in group B. Pre- and post-operative hemoglobin levels were analyzed and mean Hb levels among both the groups was 11.11+0.86 vs 11.10+0.99 g/dL that was not statistically significant (*p*-value 0.969); whereas mean Hb levels among both the groups was 9.67+0.88 vs 9.38+1.25 g/dL that was also not statistically significant (*p*-value 0.136). Quantitative analysis is reflected in table 1. Mean quantity of blood loss among both the groups was 227.55+18.12 in topical TXA group vs 262.38+17.86 in systemic TXA group. Independent sample *t*-test was used to compare quantity of blood loss among both study groups (*p*-value≤0.05). Side effects included nausea, vomiting, hypotension and hypertension were also assessed and it was observed that there was statistically significant (*p*-value≤0.05) difference in topical TXA versus systemic TXA pertaining to hypotension (*p*-value=0.000), hypertension (*p*-value=0.000) and vomiting (*p*-value=0.023). However, no significant difference was noticed for nausea (*p*-value=0.697). Detailed safety analysis is illustrated in figure 1.

Table 1: Details of demographic, analytical and clinical quantitative variables of the both study groups

Quantitative Variables	Groups	Mean	± SD
Gravida	**Group A (Topical TXA)**	3.15	1.53
	Group B (Systemic TXA)	3.41	1.29
Total Abdominal Sponges used	**Group A (Topical TXA)**	3.05	.39
	Group B (Systemic TXA)	2.98	.47
Weight (g) of abdominal sponges	**Group A (Topical TXA)**	51.85	6.58
	Group B (Systemic TXA)	51.22	7.92
Weight (g) of soaked abdominal sponges	**Group A (Topical TXA)**	63.28	10.14
	Group B (Systemic TXA)	63.53	10.51
Blood (ml) in suction bottle	**Group A (Topical TXA)**	216.50	15.16
	Group B (Systemic TXA)	249.33	15.28
Quantity of blood loss	**Group A (Topical TXA)**	227.55	18.12
	Group B (Systemic TXA)	262.38	17.86
Pre-Operative Hb	**Group A (Topical TXA)**	11.11	0.86
	Group B (Systemic TXA)	11.10	0.99
Post-Operative Hb	**Group A (Topical TXA)**	9.67	0.88
	Group B (Systemic TXA)	9.38	1.25

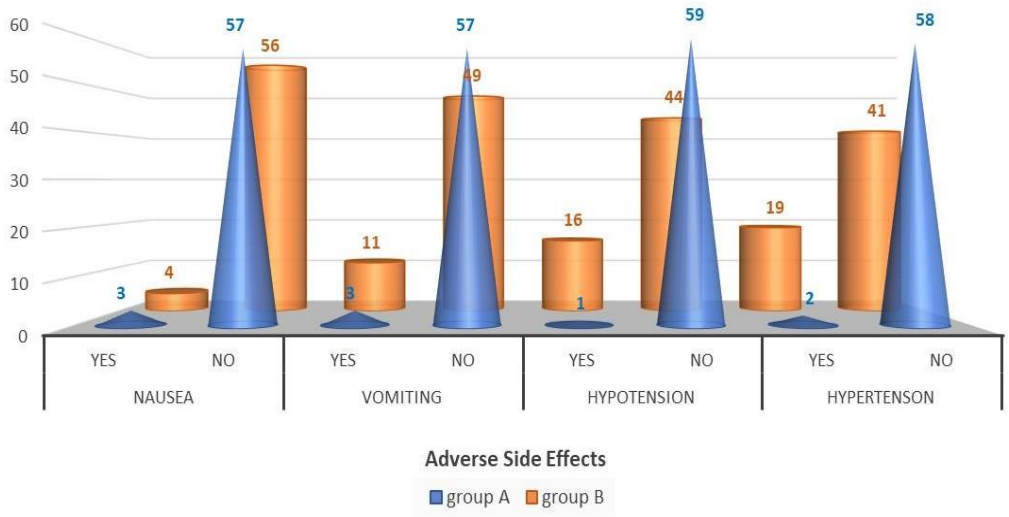

Fig.4: Incidence of adverse effects among both the study arms

DISCUSSION

The only pharmacologic intervention shown to lower PPH is the preventive injection of a uterotonic just after delivery. TXA among other antifibrinolytics works by stopping fibrinolysis and stabilizing already-existing blood clots. They thereby impede the proteolytic action of plasmin on fibrin threads by restricting the conversion of the proenzyme plasminogen to plasmin.[xx] TXA blocks lysine binding sites on plasminogen molecules reversibly.[xxi] With no notable side effects recorded, clinical studies show TXA may be useful in reducing blood loss during cesarean delivery.[xxii] Although it treats established PPH, immediate treatment is advantageous since it prevents coagulopathy.[xxiii] Though systematic reviews looking at the use of TXA in combination with standard uterotonic agents for PPH exist, [xxiv] recent clinical trials[xxv]—including the largest to date with 11,000 participants—have not yet been included in a meta-analysis. [xxvi] Moreover, little is known about high-risk individuals; only one previous meta-analysis conducted in this sensitive population was based on a small number of randomized controlled studies. [xxvii] The use of TXA in preventing PPH has been identified

as a major research priority that calls for thorough RCTs and meta-analyses of past RCTs to precisely ascertain its effectiveness for this goal. Directly contradicting multiple smaller studies that show major decreases in blood loss, [xxviii] two of the previously mentioned largest trials found no significant benefits of TXA in lowering the risk of PPH within a mostly low-risk population. Small studies are prone to biases, especially publication bias; good findings in these kinds of studies are usually not validated by later big, randomized trials.[xxix] These smaller studies raised further questions like limited power, poor randomizing techniques, and problems with allocation concealment, which might have affected the favorable results.[xxx] Meta-analyses of smaller studies are well recognized to greatly exaggerate intervention treatment effects.[xxxi] The injection of TXA before skin incision for the decrease of surgical bleeding is well-documented; thus, this strategy could also be pertinent for the prevention of PPH. Nevertheless, given the observational character of subgroup studies, these results should be regarded as hypothesis-generating and demand validation via extensive randomized controlled trials either directly comparing different times of administration or emphasizing the early administration of TXA prior to skin incision.[xxxii] Tranexamic acid's preventive use had no effect on the incidence of postpartum hemorrhage in vaginal delivery patients. Administration of tranexamic acid to individuals undergoing cesarean delivery produced a mean estimated computed blood loss reduction of over 100 ml. Regarding other clinically important outcomes, like the transfusion of blood products or the need for further surgical or radiologic procedures to control bleeding in either study, no advantages were noted. [xxxiii]

Our research has great merit in its comparative design, which directly assesses the safety and efficacy of topical rather than systemic TXA during cesarean sections. Given that it offers evidence-based analysis of the ideal TXA route of administration—a crucial factor in clinical practice—this is very important. Clinically important for lowering postpartum hemorrhage, a main cause of mother morbidity and death, the study shows that topical TXA is linked with far less blood loss than systemic TXA. Furthermore, underlined in the study is the better safety profile of topical TXA, with far fewer frequencies of side effects like hypotension and hypertension than systemic TXA. This implies that, especially for patients who run a danger of hemodynamic instability, topical TXA could be a safer substitute. Including qualitative (side effects) and quantitative (blood loss, hemoglobin levels) results helps to further strengthen the study by offering a whole picture of TXA effect.

The study has numerous restrictions notwithstanding its positives. First, the single-center study's small sample size may restrict the generalizability of the results to other settings or high-risk groups. Furthermore, although the two groups' blood loss difference was statistically significant, in the framework of cesarean sections—where blood loss can vary greatly—the therapeutic relevance of a 35 mL difference may be questionable. Important issues in obstetric practice, long-term effects or the effect of TXA on newborn health, are not also included in the study. Lastly, even if the study of side effects is exhaustive, the subjective reporting of symptoms like nausea and vomiting may restrict it among different patients. These restrictions emphasize the need of bigger, randomized controlled studies with other demographics to validate these conclusions and investigate other clinical outcomes.

CONCLUSION

This research offers important findings regarding the effectiveness and safety of topical compared to systemic TXA in the context of cesarean sections. The findings indicate that topical TXA is linked to a significant reduction in blood loss and a decreased occurrence of adverse effects, including hypotension, hypertension, and vomiting, when compared to systemic TXA. The results indicate that topical TXA may serve as a safer and effective alternative for reducing postpartum hemorrhage and enhancing maternal outcomes. The study's limitations, such as potential biases, a small sample size, and the absence of long-term or neonatal outcomes, highlight the necessity for additional research. To validate these findings and establish robust clinical guidelines for TXA administration in obstetric practice, larger randomized controlled trials involving diverse populations are essential.

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