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Original Article

Comparison of Inhalational Versus Intravenous Tranexamic Acid in the Management of Hemoptysis

Junaid Zafar, Khan Muhammad Yaqub, Sundas Shaukat*, Kamil Hussain Qureshi, Muhammad Zulqarnain Saleem**, Asif Jaleel**

Department of Anesthesia, Combined Military Hospital Rawalpindi/National University of Medical Sciences (NUMS) Pakistan,*Department of Microbiology, Rehman Medical Institute Peshawar Pakistan,**Department of Anesthesia, Pak Emirates Military Hospital /National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To assess the effectiveness of inhalational versus intravenous route administration of Tranexamic Acid for treatment of hemoptysis.

Study Design: Quasi-experimental study

Place and Duration of Study: Main Intensive Care Unit, Combined Military Hospital, Rawalpindi, Pakistan, from Aug 2022 to May 2023.

Methodology: Patients of either gender presenting to ICU with active hemoptysis with age >18 years and stable hemodynamically were included in the trial. Using a non-probability consecutive sampling technique, these participants were divided equally into two groups: Group-N (n=51), in which nebulized Tranexamic Acid was used, and Group-I (n=51), in which intravenous Tranexamic Acid was administered. Comorbidities, demographic characteristics, bleeding at 30 mins, 06 hours, and 12 hours, and adverse reactions to treatment were the parameters recorded among the groups.

Results: Gender distribution of 102 participants revealed male participants as 68(66.7%) versus 34(33.3%). The mean age of the patients in Group-N and Group-I was 48.82±8.96 years and 49.61±7.77 years, respectively. Amount of bleed after administration of Tranexamic Acid in Group-N was significantly lesser with a median amount of 0.7ml (IQR 0.5-2.0) as compared to Group-I with a median amount of 3ml (IQR 0.7-3.0) (*p*- value -0.047). Assessment of bleeding at 6 hours and 12 hours also revealed a significant reduction in Group-N compared to Group-I, with a p-value of <0.01.

Conclusion: Tranexamic Acid administered via inhalational route is more effective than the intravenous route for the treatment of hemoptysis.

Keywords: Hemoptysis, Inhalational, Intravenous, Tranexamic acid

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INTRODUCTION

Hemoptysis is a common clinical symptom observed in disorders of the respiratory system, usually caused by infectious, malignant, or traumatic events that lead to disruption and damage of the vascular system, resulting in bleeding. Hemoptysis can be minor or major, depending on the amount of blood from the airways; however, an exact cutoff value is not defined. Massive hemoptysis can result in a bleed of 100 to 1000 mL. The quantity of the bleed alone cannot define massive hemoptysis, but bleeding that leads to a critical, life-threatening condition is termed massive hemoptysis.[1,2]

This condition is self-limiting most of the times but concern about hemoptysis is of great clinical importance as this can lead to loss of a large amount of blood volume, impaired exchange of gases at the alveolar level, and resultant asphyxia, which is fatal.[3] Early diagnosis of the condition and treatment of the precipitating factors are essential in patients presenting with hemoptysis. Medical and surgical treatments are widely adopted along with resuscitative measures in patients with hemoptysis.[4]

Response to bleeding in patients activates the coagulation cascade and activation of platelets, leading to coagulation.[5] Tranexamic Acid is a common drug used in a variety of patients as an antifibrinolytic agent, which acts to inhibit plasmin. Plasmin is formed by a precursor plasminogen and activated by plasmin activator, which causes degradation of the fibrin clots. The inhibition of plasmin from binding with fibrin and causing their degradation by Tranexamic Acid makes it a very useful drug in patients who are bleeding or at risk of bleeding.[6] Tranexamic Acid has been in use in a variety of operative procedures ranging from trauma, orthopedic, gynecological and obstetrics, spine, and neurosurgeries. Oral, topical or intravenous route of administration of the drug has been used in several

Correspondence: Dr Junaid Zafar, Department of Anesthesia, Combined Military Hospital Rawalpindi Pakistan

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patients who are bleeding actively or at risk of bleeding.[7]

Besides the antifibrinolytic role of Tranexamic Acid, it has an essential role in decreasing the release of inflammatory markers like tumor necrosis factor and Interlukins and multiple trials have shown that the mortality rate and rate of systemic inflammatory response were markedly reduced with the use of Tranexamic acid. After trauma, the vascular permeability is increased, which leads to edema in the tissues, decreased perfusion, and tissue damage. The use of Tranexamic Acid has shown to reduce the chances of increased permeability by employing a protective role at a cellular level.[8,9]

Several trials have been done to assess the coagulative effectiveness of Tranexamic Acid in various surgical and non-surgical patients with a risk of bleeding.[10] The most common route of Tranexamic Acid administration in such patients was intravenous. Due to the scarcity of previous trials, our trial aims at comparing the coagulative efficacy after administration of Tranexamic Acid via the inhalational versus the intravenous route in patients with hemoptysis.

METHODOLOGY

This was a quasi-experimental study performed at the Main Intensive Care Unit, Combined Military Hospital, Rawalpindi, Pakistan, from August 2022 to May 2023 after obtaining approval from the ethical review board under ERB no 392.

The sample size calculation was performed using the WHO sample size calculator. A previous study reported that 72.72% of patients presenting with hemoptysis had cessation of bleeding within 30 minutes after administration of inhaled Tranexamic Acid, compared with 50.91% of patients when Tranexamic Acid was administered via the intravenous route.11 Using a 90% power test with a 5% level of significance, the calculated sample size for two population proportions was n=102. Using a non-probability consecutive sampling technique, participants were divided equally into two groups, i.e., Group-N (n=51), in which nebulized Tranexamic Acid was used, and Group-I (n=51), in which intravenous Tranexamic Acid was administered. (Figure)

Inclusion Criteria: Patients of either gender presenting to ICU with active hemoptysis, having an age >18 years, who are stable hemodynamically were included in the trial.

Exclusion Criteria: Patients with massive life-threatening hemoptysis who may require ventilatory support with hemodynamic instability with or without ionotropic support, requiring emergency interventions, or with a history of allergy to Tranexamic Acid were excluded from the trial.

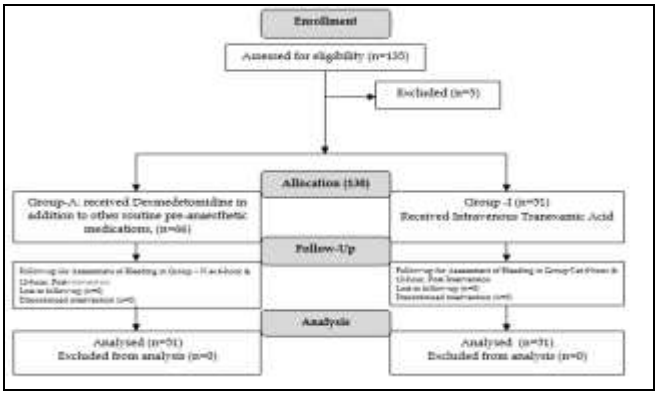

Figure: Patient flow Diagram

All participants presenting to our hospital with hemoptysis and admitted to the intensive care unit (ICU) per the inclusion criteria were included in the trial after obtaining written informed consent. Baseline vital parameters and patient characteristics were recorded. Noninvasive monitoring of vitals, including pulse oximetry, noninvasive blood pressure monitoring, electrocardiography, and temperature monitoring, was performed after admission to the ICU. Two 18- gauge intravenous lines were placed in the upper limb under aseptic conditions, and infusion of crystalloids was initiated to treat hypovolemia. Per our ICU protocol, a blood transfusion was performed after blood grouping and cross- matching when the Hb was < 8 g/dL or when bleeding was continuous and not curable with medications. Patients in Group I received intravenous Tranexamic Acid 500mg as a stat dose and then thrice daily. Patients in Group N received Tranexamic Acid via the inhalational route. 5 mL of 500 mg Tranexamic Acid was diluted in distilled water and used for nebulization at the time of admission and then thrice daily. Throughout ICU detention, vitals were continuously monitored, and patients were kept hypovolemic as indicated by a mean arterial pressure of >65 mm Hg and urine output of > 0. 5 mL/kg/hour. Tranexamic Acid was administered until the patient was stable and hemoptysis was controlled, or until discharge or a

surgical procedure for the control of bleeding. The amount of hemoptysis was evaluated using a sterile calibrated container with a designated scale indicating the amount of bleed collected in the specimen bottle. The amount of bleed was evaluated after administration of Tranexamic Acid at 30 minutes, 06 hours, and 12 hours. Patients were followed up, and adverse events such as anaphylaxis, bronchoconstriction, and embolism were noted in participants of both groups after administration of Tranexamic Acid via the inhalational and intravenous routes. The cause of the bleed was identified by the treating team and recorded while maintaining supportive care per the diagnosed disease without changing the treatment protocol for Tranexamic Acid.

Recorded data were analyzed using Statistical Package for Social Sciences (SPSS) version 23.0. Qualitative data was interpreted as frequencies and percentages, and chi square test was applied while quantitative data was interpreted as mean and standard deviation for data was normal however median and interquartile range was calculated for non-normal data. Depending on the normality of the data, parametric or non-parametric tests were applied. Data with normal distribution were assessed using independent samples t-test, while non-normal data was assessed by Man Whitney U-test to compare treatment outcomes. A *p*-value of ≤0.05 was considered as significant.

RESULTS

Gender distribution of 102 participants revealed that males were 33(64.7%) versus 35(68.6%) and females were 18(35.3%) versus 16(31.4%) in Group-N and Group-I respectively. Mean age of the patients in Group-N was 48.82 ± 8.96 years, while mean age in Group-I was 49.61±7.77 years. The most common comorbidity in participants of both groups was tuberculosis 72(70.6%) followed by malignancy, 07(6.9%), aspergillosis 04(3.9%) and others 19(18.6%). Demographic Characteristics and Comorbidities are shown in Table-I. Amount of bleed after administration of Tranexamic Acid in Group-N was significantly lesser with a median amount of 0.7ml (IQR 0.5-2) as compared to Group-I with a median amount of 3ml (IQR 0.7-3), having a *p*- value of 0.047. Assessment of bleeding at 6 hours and 12 hours also revealed a significant reduction in Group-N compared to Group-I, with a *p*-value of <0.01. Median length of hospital stay was lesser in Group-N with a median value of 3 days (IQR 2-5) as compared to Group-I with a median value of 4 days (IQR 3-6). Response to treatment among both groups is shown in Table-II. No significant adverse reactions were seen in either group; however 03(5.9%) patients developed bronchoconstriction after administration of inhalation Tranexamic Acid in Group-N.

Table–I: Demographic Characteristics and Comorbidities (n=102)

Variables		Group 'N' (n = 51)	Group 'I' (n = 51)	*p*-value
Gender N(%)	Males	33(64.7%)	35(68.6%)	0.674
	Females	18(35.3%)	16(31.4%)	
Age in years Mean±S.D		48.82 ± 8.96	49.61 ± 7.77	0.638
Comorbidities	Tuberculosis	35(68.6%)	37(72.5%)	0.741
	Malignancy	03(5.9%)	04(7.8%)	
	Aspergillosis	03(5.9%)	01(2.1%)	
	Others	10(19.6%)	09(17.6%)	

Table–II: Comparison of Treatment Outcomes (n=102)

Variables	Group 'N' (n = 51) Median (IQR)	Group 'I' (n = 51) Median (IQR)	*p*-value
Bleed at 30 mins in ml	0.7(0.5-2.0)	3.0(0.7-7.0)	0.047
Bleed at 06 hours in ml	8.0(4.0-11.0)	44.0(33.0-51.0)	<0.001
Bleed at 12 hours in ml	15.0(11.0-18.0)	53.0(29.0-70.0)	<0.001
Duration of ICU stay in days	3.0(2.0-5.0)	4.0(3.0-6.0)	0.062

DISCUSSION

This trial was conducted to assess the coagulative effectiveness of Tranexamic Acid in patients presenting with hemoptysis. Significant effectiveness of inhalational Tranexamic Acid was seen as compared to intravenously administered Tranexamic Acid. Assessment of bleeding at intervals of 30 mins revealed that the median blood loss was 0.7ml (IQR 0.5-2) as compared to Group-I with a median amount of 3ml (IQR 0.7-3), having a *p*- value of 0.047. Profound effects with better control of bleeding with nebulized Tranexamic Acid were observed at 06 hours and 12 hours after administration of Tranexamic Acid. The duration of stay in intensive care unit was decreased in the participants of Group-N with a median of 03 days (IQR 2-5) as compared to 04 days (IQR3-6) in Group-I.

Gopinath *et al.,* revealed better coagulation with nebulized as compared to intravenous use of

Tranexamic Acid in patients with hemoptysis. The participants revealed a complete cessation of bleeding after 30 mins of nebulized Tranexamic Acid administration in 73% of adult participants, as compared to 51% participants in patients receiving intravenous Tranexamic acid.[11] Another trial conducted by Bafaqih *et al.,* utilized the use of nebulized Tranexamic Acid in children presenting with alveolar hemorrhage. When Tranexamic Acid was administered via inhalational route to these participants, hemostasis was achieved with complete cessation of bleeding in 55% of the children within the next 24 hours however, when recombinant factor VIIA was given in combination with Tranexamic Acid, the hemostatic response was not very effective as compared to monotherapy of Tranexamic acid.[12]

The usual route utilized for cessation of bleeding in patients includes the use of Tranexamic Acid via the intravenous route, and trials conducted by authors like Slattery *et al.,* revealed the effective role of Tranexamic Acid in patients undergoing surgical procedures.[13] The use of Tranexamic Acid in a dose of 10mg/kg has proven effective in patients undergoing orthopedic and spine surgeries. These surgical procedures usually include massive blood loss and frequent transfusions, but the use of Tranexamic Acid via the intravenous route has been effective in decreasing the number of transfusions.[13]

Tille *et al.,* have used the intra-articular route for the administration of Tranexamic Acid, and the results of the trial were surprising as it decreased the transfusion by up to 25% in the participants with a significant decrease in blood loss during the perioperative period.[14] A similar trial conducted by Zhang et al., proposed the combined use of intravenous plus intra-articular Tranexamic Acid in patients undergoing knee surgeries. It revealed a significant reduction in the blood loss and drop in hemoglobin during the perioperative period as compared to participants who received only intravenous or intra-articular Tranexamic acid.[15]

The effectiveness of mechanism via which Tranexamic Acid performs its antifibrinolytic activity is very useful as it reduces the blood loss and the chances of deterioration, specifically in patients undergoing surgical procedures as described by Palija *et al.*[16] Different routes of administration for this drug have been devised, and trials have proven that the number of blood transfusions and the blood loss intraoperatively have been reduced significantly if the drug is given topically, intravenously, or a combination of both, regardless of the route of administration.[17]

With advances in medical science, several routes of administration for Tranexamic Acid have been described, and its anticoagulant effect has led to its use in obstetric, trauma, orthopedic, and several other surgical procedures.[18] This trial proved the effective role of Tranexamic Acid in patients with hemoptysis, and the bleed control was better achieved with inhalational use of Tranexamic Acid as compared to the intravenous route. Further trials using nebulized Tranexamic Acid to stop active bleeding are required.

LIMITATION OF STUDY

This quasi-experimental study is limited by the lack of randomization and blinding, which may have introduced selection and observer bias between the treatment groups. Additionally, the single-center setting with a limited sample size and short follow-up period may restrict the generalizability of the findings.

CONCLUSION

Administering Tranexamic Acid through inhalation proves to be more effective than the intravenous route for treating hemoptysis. This method not only enhances the delivery of the medication directly to the lungs but also maximizes its therapeutic benefits, providing a targeted approach to managing this potentially life-threatening condition.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

JZ & KMY: Data acquisition, data analysis, critical review, approval of the final version to be published.

SS & KHQ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MZS & AJ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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