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EVALUATION OF TOTAL BLOOD LOSS AFTER ADMINISTRATION OF TRANEXAIC ACID IN TOTAL HIP ARTHROPLASTY

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Abstract

Total arthroplasty is one of the most frequent procedures in orthopedic surgery, proven to be an effective treatment that significantly improves patients' quality of life. However, it is associated with considerable perioperative blood loss which can lead to suboptimal outcomes and systemic complications. The aim of this study is to assess the total blood loss after the application of tranexamic acid in patients undergoing total hip arthroplasty surgery. A total of 64 patients were included, divided into two groups: a test group where tranexamic acid was administered intravenously and a control group where tranexamic acid was not used. The values for total blood loss and erythrocyte volume loss were statistically significantly lower in the test group. Blood loss in the control group was higher by an average of 482.19 ml. Erythrocyte loss in the control group was higher by an average of 256.28 ml. The use of tranexamic acid as a standard protocol in total hip arthroplasty is a safe and effective method to reduce total blood loss. Ultimately, this results in a reduced need for blood transfusion, a decrease in potential risks and complications associated with it, and the achievement of pharmacoeconomic benefits.

Key words: total hip arthroplasty, tranexamic acid

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Introduction

Total hip arthroplasty (THA) is a major orthopedic surgery and the only definitive treatment for advanced hip osteoarthritis. It is associated with significant perioperative blood loss, which can lead to unsatisfactory outcomes and systemic complications, especially in older individuals [1,2]. Due to the high incidence of hip osteoarthritis, THA is one of the most frequent interventions in orthopedic surgery with proven effective results, significantly improving the quality of life for patients [3]. In the 1960s, THA revolutionized the treatment of osteoarthritis. Advances in bioengineering technology, prosthesis design, materials, fixation durability (both cemented and cementless prostheses), and minimally invasive surgery have resulted in excellent long-term outcomes. It is no coincidence that THA is considered the surgery of the century [4].

One of the most common problems in THA is excessive bleeding and the large need for blood transfusion [5]. Blood loss ranges from 1188 mL to 2000 mL [6,7,8,9,10]. However, it is difficult to compare these values as there are many different formulas for calculating blood loss. The prevalence of allogeneic erythrocyte transfusion reported by various authors ranges from 21% to 70% [11,12,13,14]. Blood transfusion is sometimes life-saving but is associated with numerous risks, including transfusion-related lung injury, immunomodulation, pathogen transmission, and wound infection [15,16,17]. Several methods are used to reduce blood loss and, consequently, the need for transfusion, such as blood salvage, improved surgical hemostasis techniques, minimally invasive surgery, and erythropoiesis stimulation with epoetin alpha. These methods have proven effective, but each incurs additional costs [18].

Recently, pharmacological substances known as antifibrinolytics have been tested to minimize blood loss in THA. Particularly, tranexamic acid, which is 7 to 10 times more potent in inhibiting fibrinolysis than epsilon-aminocaproic acid [19]. Tranexamic acid is a synthetic analogue of the amino acid lysine, known for its inhibition of fibrinolysis by reversibly binding to 4 to 5 lysine receptor sites on plasminogen. This reduces the conversion of plasminogen to plasmin, preventing fibrin degradation and preserving the fibrin matrix structure. This slows

down the process of fibrinolysis [20]. Tranexamic acid does not systemically affect coagulation, does not alter platelet count or function, nor does it affect activated partial thromboplastin time or prothrombin time. After an intravenous bolus dose of 1 gram, maximum plasma concentrations are achieved within 5 to 15 minutes, and it quickly diffuses into synovial fluid and synovial membranes. Therapeutic plasma concentrations required for an 80% reduction in plasminogen activity are 10 ng/ml. The intravenous dose of tranexamic acid at 10 mg/kg of ideal body weight maintains these concentrations in plasma for up to 3 hours. After intravenous administration, the elimination of tranexamic acid follows a triphasic exponential phase, with over 95% excreted unchanged in the urine. The total cumulative excretion of the drug after intravenous dosing is about 90% within 24 hours. The drug crosses the blood-brain barrier and rapidly penetrates the joint fluid and synovial membranes. Excretion into breast milk is low, constituting only 1% of the plasma peak concentration. It also crosses the placental barrier. Tranexamic acid is well-tolerated, and side effects are rare, usually manifesting as nausea or diarrhea. There are no mutagenic effects or adverse consequences for the fetus. Retinal changes that may occur with toxic doses do not appear with therapeutic doses. Color perception disturbances may occur, and in such cases, therapy should be discontinued immediately. It can be administered intravenously, orally, and locally [21,22]. Although there is growing interest in the use of tranexamic acid to minimize blood loss, there is still no widely accepted protocol for its use in total hip arthroplasty.

Materials and Methods

This study is a prospective, single-center, clinical trial. Informed consent for voluntary participation in the study and the procedure itself was obtained from the patients who underwent total cementless hip arthroplasty. The research was conducted at the University Clinic for Orthopaedic Diseases in Skopje, over a period of 12 months, involving 64 patients over the age of 18, in whom the diagnosis of hip osteoarthritis was clinically and radiographically confirmed, with an indication for surgical treatment. Only patients with normal hematologic status and hemostasis were included. Patients were excluded if they had: coagulopathy, rheumatoid arthritis, chronic anticoagulant and corticosteroid therapy, infectious diseases, malignancies, the

need for revision surgery, hypersensitivity to tranexamic acid, coronary or vascular stents placed for less than 6 months, deep vein thrombosis, fixation of endoprosthesis components with bone cement, or intravenous or oral tranexamic acid therapy during treatment.

Prior to surgery, all patients had their height and weight measured, a complete blood count, hemostasis tests, and an evaluation by the anesthesiologist. All patients received antibiotic and antithrombotic prophylaxis with low molecular weight heparin according to protocol. A Watson-Jones anterior-lateral approach to the proximal femur was used. The patients were randomly divided into two groups. The first group was the control group, while the second group was the experimental group, each consisting of 32 patients. In the control group, the established surgical protocol for total hip arthroplasty at the Orthopedic Clinic in Skopje was followed. In the experimental group, tranexamic acid was administered before the skin incision, according to the recommended dosage, i.e., 1 gram of tranexamic acid via slow intravenous infusion (=1 ml/min). The indication for intraoperative erythrocyte transfusion was determined by the anesthesiologist. The indication for postoperative erythrocyte transfusion was set when the hemoglobin level dropped below 9 g/dL or when the patient exhibited clinical signs of anemia, such as fatigue, palpitations, pallor, tachycardia, tachypnea, and hypotension.

During the study, preoperative values of erythrocytes, hemoglobin, and hematocrit were recorded. Postoperative values recorded included the volume of the drainage pump on the day of surgery and the first postoperative drain, measured using a digital scale, as well as the values of erythrocytes, hemoglobin, hematocrit on the second and fifth postoperative day and the number of transfusions. The total blood loss (TBL) was calculated using the Mercuriali formula. The total blood volume (TBV) was calculated using the Nadler formula in milliliters, multiplied by the difference between the preoperative hematocrit and the hematocrit on the fifth postoperative day. In case of a transfusion, the volume of erythrocyte transfusion in milliliters was added to the calculation [23,24]. The total blood loss using the Mercuriali formula is expressed in milliliters of erythrocytes. To convert milliliters of erythrocytes to milliliters of blood, the volume of lost erythrocytes is divided by the average hematocrit and multiplied by 100 [25].

$$TBL = (TBV) \times (Hct_{preop.} - Hct_{5th\ postop.\ day}) + \text{erythrocyte transfusion in ml}$$

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For the calculation of TBV, the following formulas were used:

For males:

$$TBV = k1 \times h^3 + k2 \times w + k3$$

where k1 = 0.3669, k2 = 0.03219, k3 = 0.6041

For females:

$$TBV = k1 \times h^3 + k2 \times w + k3$$

where k1 = 0.3561, k2 = 0.03308, k3 = 0.1833

h = height in meters;

w = weight in kilograms.

Results

This study included 64 patients, of which 32 (50%) were male and 32 (50%) were female. The patients involved in the study were aged from 43 to 76 years, with an average age of 62.23 years. The demographic data of the patients are presented in Table 1.

Table 1. Demographic data of the patients in the experimental and control groups

$\bar{x} \pm SD$

(The values are statistically significant at $p < 0.05$)

Group	**Experimental**	**Control**	**Significance**
Age (years)	63.06±8.61	61.41±6.82	NO
Body Mass Index	29.720±3.28	30.035±4.45	NO
Gender (male/female)	16/16	16/16	NO

t- test, No – no statistically significant difference; Yes – statistically significant at $p < 0.05$

Patients in the experimental group are older and lighter, but without statistical significance. Men and women are equally represented in both groups.

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As part of the preoperative preparation, a complete blood count was performed for all patients. The preoperative values of erythrocytes, hemoglobin, and hematocrit in the groups are presented in Table 2.

Table 2. Demographic data of the patients in the experimental and control groups
$\bar{x} \pm SD$

Group	**Experimental**	**Control**	**Significance**
Erythrocytes 10^{12}/L	4.5219±0.4326	4.7003±0.3761	NO
Hemoglobin g/L	134.03±12.10	139.72±12.21	NO
Hematocrit	0.40481±0.03460	0.41009±0.03831	NO

(The values are statistically significant at $p < 0.05$)

The average values of erythrocytes, hemoglobin, and hematocrit were higher in the control group, but without a statistically significant difference.

In the study, the total blood loss expressed in milliliters of erythrocytes was calculated using the Mercuriali formula, and then converted into milliliters of blood. Table 3 shows the average blood loss in both groups and the statistical significance.

Table 3. Average blood loss

Group	**Experimental**		**Control**		**Significance**
	$\bar{x}$	SD	$\bar{x}$	SD	
Erythrocytes (ml)	474.91	216.07	731.19	227.49	Yes
Blood (ml)	1331.31	486.74	1813.50	537.35	Yes

t- test, No – no statistically significant difference; Yes – statistically significant at $p < 0.05$

The values for total blood loss and erythrocyte loss volume were statistically significantly lower in the patients in the experimental group. Blood loss in the control group was higher by an average of 482.19 ml. Erythrocyte loss in the control group was higher by an average of 256.28 ml.

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During the study, the number and timing of blood transfusions were recorded. Table 4 shows the distribution of transfusions performed during the intraoperative and postoperative periods.

Table 4**.** Distribution of intraoperative and postoperative blood transfusions

Group	**Experimental**	**Control**
Intraoperative transfusion	2	4
Postoperative transfusion	5	25
Total	7	29

During the intraoperative period, 4 blood transfusions were performed in the control group, which is 2 more than the number of transfusions performed in the experimental group. During the postoperative period, the number of transfusions was significantly higher in the control group. In the control group, 25 blood transfusions were performed during the postoperative period, while in the experimental group, 5 blood transfusions were administered.

Discussion

Tranexamic acid is a synthetic amino acid that acts as a competitive inhibitor of plasminogen and reduces fibrinolysis. Surgical trauma promotes the release of tPA (tissue plasminogen activator), which activates fibrinolysis. Fibrinolysis is a process that is normally inhibited 24 hours after surgery. However, antifibrinolytics such as tranexamic acid can block the conversion process of plasminogen to plasmin in the early stages, thereby reducing postoperative blood loss. Tranexamic acid is an antifibrinolytic agent with the potential to significantly change how blood loss is managed during total hip arthroplasty. Tranexamic acid has been used in total hip arthroplasty since 2000, but a standardized protocol has not yet been established due to the high variability in administration methodology, dosage, duration, and timing of administration. Tranexamic acid is well tolerated, and adverse effects are rare, usually

manifesting as nausea or diarrhea. It has no mutagenic effects or adverse consequences for the fetus. Retinal changes that may occur with toxic doses do not appear when therapeutic doses are used [26,27].

In this study, the results obtained from both groups show a significant difference. The experimental group had less blood loss by an average of 482.19 ml and less erythrocyte loss by an average of 256.28 ml.

According to the results, the use of tranexamic acid in total hip arthroplasty results in significantly lower blood loss. This will lead to a reduced need for transfusions, and consequently, reduce the adverse effects and risks associated with transfusions, thus achieving a pharmacoeconomic benefit.

Conclusion

The use of tranexamic acid as a standard protocol in total hip arthroplasty is a safe and effective way to reduce total blood loss. This would ultimately result in a reduced need for blood transfusions, a decrease in potential risks and complications associated with transfusions, and the achievement of a pharmacoeconomic benefit.

References

[1] A. Saleh, T. Small, A.L. Chandran Pillai, N.K. Schiltz, A.K. Klika, W.K. Barsoum, Allogenic blood transfusion following total hip arthroplasty: results from the nationwide inpatient sample, 2000 to 2009, J. bone Jt. Surg. Am. 96 (18) (2014) e155.

[2] [2] B.E. Bierbaum, J.J. Callaghan, J.O. 2.Galante, H.E. Rubash, R.E. Tooms, R.B. Welch, An analysis of blood management in patients having a total hip or knee arthroplasty, J. Bone Jt. Surg. Am. 81 (1) (1999) 2e10.

[3] Räsänen P, Paavolainen P, Sintonen H, Koivisto AM, Blom M, Ryynänen OP, Roine RP. Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. Acta Orthop. 2007 Feb;78(1):108-15. doi: 10.1080/17453670610013501. PMID: 17453401.

[4] Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. Lancet. 2007 Oct 27;370(9597):1508-19. doi: 10.1016/S0140-6736(07)60457-7. PMID: 17964352.

[5] Vuille-Lessard E, Boudreault D, Girard F, Ruel M, Chagnon M, Hardy JF. Red blood cell transfusion practice in elective orthopedic surgery: a multicenter cohort study. Transfusion. 2010 Oct;50(10):2117-24. doi: 10.1111/j.1537-2995.2010.02697.x. Epub 2010 Oct 4. PMID: 20492612.

[6] Hays MB, Mayfield JF. Total blood loss in major joint arthroplasty. A comparison of cemented and noncemented hip and knee operations. J Arthroplasty. 1988;3 Suppl:S47-9. doi: 10.1016/s0883-5403(88)80008-1. PMID: 3199139.

[7] Sehat KR, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. J Bone Joint Surg Br. 2004 May;86(4):561-5. PMID: 15174554.

[8] Billote DB, Glisson SN, Green D, Wixson RL. A prospective, randomized study of preoperative autologous donation for hip replacement surgery. J Bone Joint Surg Am. 2002 Aug;84(8):1299-304. doi: 10.2106/00004623-200208000-00002. PMID: 12177257.

[9] Charrois O, Kahwaji A, Vastel L, Rosencher N, Courpied JP. Blood loss in total hip arthroplasty for rapidly destructive coxarthrosis. Int Orthop. 2001;25(1):22-4. doi: 10.1007/s002640000210. PMID: 11374262; PMCID: PMC3620609.

[10] Zha, GC., Zhu, XR., Wang, L. *et al*. Tranexamic acid reduces blood loss in primary total hip arthroplasty performed using the direct anterior approach: a one-center retrospective observational study. *J Orthop Traumatol* **23**, 12 (2022). https://doi.org/10.1186/s10195-022-00638-7

[11] Stanworth SJ, Cockburn HA, Boralessa H, Contreras M. Which groups of patients are transfused? A study of red cell usage in London and southeast England. Vox Sang. 2002 Nov;83(4):352-7. doi: 10.1046/j.1423-0410.2002.00237.x. PMID: 12437523.

[12] Jans Ø, Kehlet H, Hussain Z, Johansson PI. Transfusion practice in hip arthroplasty--a nationwide study. Vox Sang. 2011 May;100(4):374-80. doi: 10.1111/j.1423-0410.2010.01428.x. Epub 2010 Oct 28. PMID: 21029109.

[13] Browne JA, Adib F, Brown TE, Novicoff WM. Transfusion rates are increasing following total hip arthroplasty: risk factors and outcomes. J Arthroplasty. 2013 Sep;28(8 Suppl):34-7. doi: 10.1016/j.arth.2013.03.035. Epub 2013 Jul 26. PMID: 23896359.

[14] BIERBAUM, BENJAMIN E. M.D.†, CHESTNUT HILL, MASSACHUSETTS; CALLAGHAN, JOHN J. M.D.‡, IOWA CITY, IOWA; GALANTE, JORGE O. M.D., D.M.SC.§, CHICAGO, ILLINOIS; RUBASH, HARRY E. M.D.#, BOSTON, MASSACHUSETTS; TOOMS, ROBERT E. M.D.**, MEMPHIS, TENNESSEE; WELCH, RICHARD B. M.D.††, SAN FRANCISCO, CALIFORNIA. An Analysis of Blood Management in Patients Having a Total Hip or Knee Arthroplasty*. The Journal of Bone & Joint Surgery 81(1):p 2-10, January 1999.

[15] Spiess BD. Transfusion of blood products affects outcome in cardiac surgery. Semin Cardiothorac Vasc Anesth. 2004 Dec;8(4):267-81. doi: 10.1177/108925320400800402. PMID: 15583789.

[16] Rawn J. The silent risks of blood transfusion. Curr Opin Anaesthesiol. 2008 Oct;21(5):664-8. doi: 10.1097/ACO.0b013e32830f1fd1. PMID: 18784496.

[17] 13. Taneja A, El-Bakoury A, Khong H, Railton P, Sharma R, Johnston KD, Puloski S, Smith C, Powell J. Association between Allogeneic Blood Transfusion and Wound Infection after Total Hip or Knee Arthroplasty: A Retrospective Case-Control Study. J Bone Jt Infect. 2019 Apr 20;4(2):99-105. doi: 10.7150/jbji.30636. PMID: 31192107; PMCID: PMC6536767.

[18] Juraj M, Jaroslav V, Gažová A, Žufková V, Kyselovič J, Šteňo B. Evaluation of efficacy and safety of systemic and topical intra-articular administration of tranexamic acid in primary unilateral total hip arthroplasty. Medicine (Baltimore). 2021 Jul 2;100(26):e26565. doi: 10.1097/MD.0000000000026565. PMID: 34190197; PMCID: PMC8257841.

[19] Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol Suppl (R Coll Pathol). 1980;14:41-7. PMID: 7000846; PMCID: PMC1347104.

[20] Cai J, Ribkoff J, Olson S, Raghunathan V, Al-Samkari H, DeLoughery TG, Shatzel JJ. The many roles of tranexamic acid: An overview of the clinical indications for TXA in

medical and surgical patients. Eur J Haematol. 2020 Feb;104(2):79-87. doi: 10.1111/ejh.13348. Epub 2019 Dec 16. PMID: 31729076; PMCID: PMC7023891.

[21] Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol.1980; 33(14): 41-47.

[22] Dunn CJ, Goa KL. Tranexamic Acid. A Rewiew of its Use in Surgery and Other indications. Drugs.1999; 75(6):1005-32.

[23] Mercuriali F, Inghilleri G. Proposal of an algorithm to help the choice of the best transfusion strategy. Curr Med Res Opin. 1996;13(8):465–478. https://doi.org/ 10.1185/03007999609115227.

[24] Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51(2):224–232.

[25] Gibon E, Courpied JP, Hamadouche M. Total joint replacement and blood loss: what is the best equation? Int Orthop. 2013 Apr;37(4):735-9. doi: 10.1007/s00264-013-1801-0. Epub 2013 Feb 6. PMID: 23385607; PMCID: PMC3609988.

[26] Wei W, Wei B. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. J Arthroplasty. 2014 Nov;29(11):2113-6. doi: 10.1016/j.arth.2014.07.019. Epub 2014 Jul 30. PMID: 25155138.

[27] Ekbäck, Gustav MD*; Axelsson, Kjell MD, PhD*; Ryttberg, Lars MD†; Edlund, Bror MD, PhD‡; Kjellberg, Jill Chief CRNA*; Weckström, Johan MD†; Carlsson, Olle PhD§; Schött, Ulf MD, PhD*. Tranexamic Acid Reduces Blood Loss in Total Hip Replacement Surgery. Anesthesia & Analgesia 91(5):p 1124-1130, November 2000. | DOI: 10.1213/00000539-200011000-00014