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Topical intra articular tranexamic acid reduces packed blood cell consumption in total joint arthroplasty

El ácido tranexámico intraarticular tópico reduce el consumo de glóbulos rojos concentrados en la artroplastía articular total

Fraind-Maya G,* Nasrawy T,* Kandel L,* Greenberg A,* Liebergall M,* Perets I,* Laniado-Nahmad D,* Rivkin G*

Orthopedic Surgery Department, Hadassah Hebrew University Hospital. Jerusalem, Israel.

ABSTRACT. Introduction: post-operative blood loss anemia is an undesired event following total joint arthroplasty. Use of tranexamic acid (TXA) has been shown to reduce blood loss after surgery and can be administered intravenously, orally and topically. We assessed the effect of topical intra articular TXA administration at the end of surgery in total joint arthroplasty on post-operative packed blood cell units' consumption. **Objective:** assess the effect of topical intra-articular TXA administration in reduction of packed blood cell units' consumption postoperatively. **Material and methods:** this is a retrospective study comparing two groups of patients that had either a primary total knee arthroplasty (TKA) or primary total hip arthroplasty (THA) during a four months' period before and after the beginning of intra articular administration of a solution containing 2 grams of TXA. Pre-operative hemoglobin level, post-operative day one hemoglobin level, packed blood cell administration and venous thromboembolism events (VTE) were assessed. **Results:** a total of 282 patients were reviewed, 148 records of patients that had a TKA and 134 records of patients that had THA. There were 80 and 68 TKA without and with TXA administration, respectively. There were 84 and 50 THA without and with TXA administration, respectively. There was no difference between the groups with regard to preoperative anticoagulation and aspirin treatment and VTE risk assessment. There was also no difference regarding

RESUMEN. Introducción: la anemia por pérdida de sangre postoperatoria es un evento no deseado tras una artroplastía articular total. Se ha demostrado que el uso de ácido tranexámico (TXA) reduce la pérdida de sangre tras la cirugía y puede administrarse por vía intravenosa, oral y tópica. Evaluamos el efecto de la administración tópica intraarticular de TXA al final de la cirugía en la artroplastía articular total sobre el consumo de las unidades de células sanguíneas empaquetadas postoperatorias. **Objetivo:** evaluar el efecto de la administración tópica intraarticular de TXA en la reducción del consumo de unidades de células sanguíneas empaquetadas tras la operación. **Material y métodos:** este es un estudio retrospectivo que compara dos grupos de pacientes que se sometieron a una artroplastía primaria total de rodilla (ATR) o una artroplastía primaria total de cadera (ATC) durante un período de cuatro meses antes y después del inicio de la administración intraarticular de una solución que contenía 2 gramos de TXA. Se evaluaron los niveles preoperatorios de hemoglobina, el nivel de hemoglobina del primer día postoperatorio, la administración de células sanguíneas empaquetadas y los eventos de tromboembolismo venoso (TEV). **Resultados:** se revisaron un total de 282 pacientes, 148 registros de pacientes con una ATR y 134 registros de pacientes con ATC. Había 80 y 68 ATR sin y con administración de TXA, respectivamente. Había 84 y 50 ATC sin y con administración de la TXA, respectivamente. No hubo diferencias entre los grupos en cuanto al tratamiento

* Orthopedic Surgery Department, Hadassah Hebrew University Hospital. Jerusalem, Israel.

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Correspondence:
Gabriel Fraind Maya
E-mail: fraind29@gmail.com

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preoperative hemoglobin levels. Patients undergoing THA and TKA showed a significant decrease in the hemoglobin level between preoperative levels to hemoglobin on post-operative day. However, administration of TXA ameliorated this decrease in hemoglobin levels, from 2.77 to 2.18 g/dl in hip arthroplasty ($p < 0.001$) and from 2.92 to 1.72 g/dl in knee arthroplasty ($p < 0.001$). In the THA group 13 packed blood cell units were administered without TXA compared to two units in patients treated with TXA ($p < 0.001$). In the TKA group 15 packed blood cell units were administered without TXA compared to two units in patients treated with TXA ($p < 0.001$). There were no VTE events in the THA patients. In the TKA patients, pulmonary embolism was diagnosed in two patients not treated with TXA and in three patients that were treated with intra articular TXA ($p = 0.66$). **Conclusion:** intra-articular topical administration of TXA at the end of surgery significantly reduced need for post-operative packed blood cell units' administration without increases in VTE risk in all patients undergoing primary THA and TKA.

Keywords: tranexamic acid, bleeding, packed-cells, arthroplasty, venous thromboembolism.

preoperatorio de anticoagulación y aspirina ni en la evaluación de riesgos de TEV. Tampoco hubo diferencia en los niveles de hemoglobina preoperatorios. Los pacientes sometidos a ATC y ATR mostraron una disminución significativa del nivel de hemoglobina entre los niveles preoperatorios y la hemoglobina en el día postoperatorio. Sin embargo, la administración de TXA mitigó esta disminución de los niveles de hemoglobina, pasando del 2.77 al 2.18 g/dl en la artroplastía de cadera ($p < 0.001$) y del 2.92 al 1.72 g/dl en la artroplastía de rodilla ($p < 0.001$). En el grupo de ATC se administraron 13 unidades de células sanguíneas empaquetadas sin TAX en comparación con dos unidades en pacientes tratados con TXA ($p < 0.001$). En el grupo ATR se administraron 15 unidades de células sanguíneas empaquetadas sin TXA, en comparación con dos unidades en pacientes tratados con TXA ($p < 0.001$). No hubo eventos de TEV en los pacientes con ATC. En los pacientes con ATR, se diagnosticó embolia pulmonar en dos pacientes no tratados con TXA y en tres pacientes tratados con TXA intraarticular ($p = 0.66$). **Conclusión:** la administración intraarticular tópica de TXA al final de la cirugía redujo significativamente la necesidad de administración de unidades de células sanguíneas empaquetadas postoperatorias sin aumentar el riesgo de TEV en todos los pacientes sometidos a ATC primaria y ATR.

Palabras clave: ácido tranexámico, sangrado, células empaquetadas, artroplastía, tromboembolismo venoso.

Abbreviations:
IM = intramuscular.
IV = intravenous.
THA = total hip arthroplasty.
TKA = total knee arthroplasty.
TXA = tranexamic acid.
VTE = venous thromboembolism events.

Introduction

Aging population and advances in total joint arthroplasty led to an increase in the number of knee and hip arthroplasties during the last two decades and are expected to continue to increase in the near future. Over 900,000 cases of THA and TKA are performed every year in the US.[1,2]

Peri-operative blood loss is a concern following knee and hip arthroplasty surgery. It is estimated by different studies in the literature to be between 700 ml-2 l in these procedures (2.2-3.8 g/dl) leading to acute anemia.[2,3,4,5,6,7,8] Around 11-67% of the patients will require blood transfusion after THA and TKA.[1,9]

Blood transfusions can cause allergic reactions, infections, anaphylaxis and further complications resulting in higher cost and longer hospitalization for the patients.[1,2,4,5,10]

Preventive techniques had been proposed to minimize the risk of blood loss, such as autologous blood transfusion or use of autologous fibrin, tourniquet (in TKA), intraoperative blood saving methods and hypotensive anesthesia, however, the use of tranexamic acid took special attention in recent research.[8,11,12] Tranexamic acid, a synthetic competitive antifibrinolytic agent has been used in recent years as a method to decrease peri-operative blood loss.

The aim of this study was to describe our results of TXA administration through the drain in a group of patients in which TXA was administrated and a group of patients where TXA was not used in patients undergoing knee or hip arthroplasty.

Material and methods

This was a retrospective study. We started using TXA in all patients undergoing hip and knee replacement in January 2016. We compared two groups of patients, all the patients that had primary knee and hip replacement during the time between February to June 2015 (before the start of TXA treatment) and all patients that had primary knee and hip replacement between February to June 2016 (after TXA treatment became standard protocol).

The tranexamic acid was administered routinely in both cases in a retrograde manner through a drain placed prior to the closure of the wound beneath the fascia and was closed for a period of two hours, which is the half-life of the TXA. It was then opened and placed on negative pressure suction.

Demographic data collected included age, gender, side and surgery. Pre-operative hemoglobin levels as well as those obtained on the first post-operative day per our standard routine were collected as well as the number of packed blood cells ordered and transfused.

The transfusion criteria were based on the decision of the on-call orthopedic surgeon, considering clinical symptoms related to anemia on an individualized basis, such as fatigue, weakness, pallor, tachycardia, drowsiness, and shortness of breath. Additionally, hemoglobin criteria were used, with reference values of above 8-9 g/dl in patients without cardiac history and above 9-10 g/dl in patients with a cardiac history.

The patients were classified as high risk factor patients in case of previous venous thrombotic events or any anticoagulant used for any indication, otherwise were treated as non-risk patients.

Every primary THA o TKA where included, excluding fractures, tumor prosthesis, periprosthetic fractures, revisions and bilateral procedures.

Results

A total of 282 patients were included in this study. Every single one was treated by an attending surgeon with subspecialty in joint replacements. In 2015, 164 patients underwent knee and hip arthroplasties: 80 and 84 respectively. In 2016, 118 patients underwent knee and hip arthroplasties: 68 and 50 respectively. There was no statistical significance between the groups in respect to preoperative use of anticoagulants, aspirin and risk for VTE *(Table 1)*.

In THA a standard posterolateral approach was perform in all cases and a standard anterior approach for the TKA and medial parapatellar arthrotomy with using extramedullary guiding cut and torniquet.

In patients undergoing total knee arthroplasty the pre-operative hemoglobin levels were 13.36 g/dl among patients not receiving TXA and 13.54 g/dl among those treated with TXA. Hemoglobin levels recorded on the first post-operative day were 10.4 and 11.8 g/dl for patients not treated with TXA and those that were treated with TXA, respectively *(Table 2)*.

In patients undergoing total hip arthroplasty the pre-operative hemoglobin levels were 13.11 g/dl among patients not receiving TXA and 13.49 g/dl among those treated with TXA. Hemoglobin levels recorded on the first post-operative day were 10.34 and 11.31 g/dl for patients not treated with TXA and those that were treated with TXA, respectively *(Table 2)*.

Mean hemoglobin levels reduction was 2.92 vs 1.7 g/dl for patients undergoing knee arthroplasties without and with TXA treatment respectively. That difference was statistically significant ($p < 0.001$).

Mean hemoglobin levels reduction was 2.76 vs 2.18 g/dl for patients undergoing hip arthroplasties without and with TXA treatment respectively. That difference was statistically significant ($p < 0.001$).

Packed blood cells transfusions were given to 15 patients undergoing knee arthroplasty without TXA treatment compared with two patients treated with TXA ($p = 0.003$).

Packed blood cells transfusions were given to 13 patients undergoing hip arthroplasty without TXA treatment compared with two patients treated with TXA ($p = 0.05$).

Table 1: Baseline demographic and clinical data.

	Total knee arthroplasty		
	Control group N = 80 n (%)	Tranexamic acid group N = 68 n (%)	p*
Age‡	71.39 ± 8.74	69.98 ± 8.69	0.331
Sex			
Male	23	24	
Female	57	44	
Non risk factor patients	58 (72.5)	51 (75)	
Previous VTE or anticoagulant	22 (27.5)	17 (25)	
	Total hip arthroplasty		
	Control group N = 84 n (%)	Tranexamic acid group N = 50 n (%)	p*
Age‡	62.91 ± 13.31	65.46 ± 13.61	0.290
Sex			
Male	29	23	
Female	55	27	
Non risk factor patients	70 (83.33)	37 (74)	
Previous VTE or anticoagulant	14 (16.66)	13 (26)	

* Students t-test. ‡ Mean ± standard deviation. VTE = venous thromboembolism.

Table 2: Blood loss, hematologic data, and allogeneic blood transfusions.

		Total knee arthroplasty		
		Control group N = 80	Tranexamic acid group N = 68	p*
Preoperative Hb‡		13.36 ± 1.43	13.54 ± 1.26	
POD 1 Hb‡		10.44 ± 1.46	11.83 ± 1.18	≤ 0.001
Hb Reduction‡		2.92 ± 0.93	1.71 ± 0.82	
Packed RBC transfusions		23 PC	2 PC	≤ 0.001
	1 PC	9 patients	2 patients	
	2 PC	4 patients		
	3 PC	1 patient		
Non-risk vs previous VTE PC consumption, (patients)		(5 vs 9)	(2 vs 0)	
Post-op complications		2 (pulmonary embolism)	Non	
		Total hip arthroplasty		
		Control group N = 84	Tranexamic acid group N = 50	p*
Preoperative Hb‡		13.11 ± 1.22	13.49 ± 1.55	
POD 1 Hb‡		10.34 ± 1.23	11.31 ± 1.39	≤ 0.001
Hb Reduction‡		2.76 ± 0.88	2.179 ± 1.08	
Packed RBC transfusions		17 PC	2 patients	≤ 0.001
	1 PC	10 patients	2 patients	
	2 PC	2 patients		
	3 PC	1 patient		
Non-risk vs. previous VTE PC consumption, (patients)		(9 vs. 4)	(2 vs. 0)	
Post-op complications		Non	Non	

* p-values. ‡ Mean ± standard deviation.
PC = packed cells. POD 1 Hb = post-operative day one hemoglobin. RBC = red blood cells. VTE = venous thromboembolism.

Pulmonary embolism was diagnosed in two patients that underwent knee arthroplasty and did not receive TXA compared with three that had knee arthroplasty and TXA (p = 0.661).

There were no venous thromboembolism complications in patients that underwent hip arthroplasty.

Discussion

In the past decades the tranexamic acid (TXA), a synthetic competitive antifibrinolytic agent, that blocks the lysine-binding sites of plasminogen, resulting in clot stabilization, has been applied successfully to control bleeding.[1,3,4,6,8,9,11,12,13,14] It was first described in cardiothoracic surgery showing great results, after that its' use spread to other disciplines.[1,4,10]

This clot stabilization might suggest that use of TXA might lead to a higher risk of venous thrombotic events (VTE). Several studies disproved this alleged correlation.[2,3,6,10]

Whiting et al in a retrospective study concluded that even patients with a higher risk for VTE - those with previous thrombotic events, cardio/coagulopathy's and patients with previous cardiac procedure - had no increased risk for VTE after using TXA.[15]

Tranexamic acid can be administered in several ways. Intravenous (IV) and topical are most commonly used. Oral and intramuscular (IM) administration have also been described.[8]

Tranexamic acid active biological half-life is three hours with 90% excretion in two hours.[9] Maximal plasma levels are reached within 5-15 minutes in IV administration, 30 minutes in IM administration and two hours after oral administration.

Sarzaeem et al. in a randomized and double-blind study of 200 patients, compared the use of TXA: IV, topical application and injection through the drain. They showed significantly less blood loss in the three groups that used TXA compared to control group. Among them, intra-articular administration TXA through the drain showed better results with decrease of 80% of the bleeding, then the IV group with reduction of 45% and topical with 14%.[9] Poeran et al.[7] performed a retrospective cohort study in 510 hospitals in the US including 872,416 patients that underwent TKR and THR showing a significant reduction blood transfusion rate after surgery without increasing the risk of complications including VTE.[7] Also, they reported decrease of admission for intensive care unit from 7.5 to 3.1%.[7] Kim et al reviewed 28 randomized controlled trials using TXA in TKR (22 with IV administration and six with topical) concluding that both systematic and topical administration reduced post-operative bleeding. They found only two studies that compared the use of topical vs IV TXA administration, one of them showing similar results and the

second showing the topical group to be superior in blood loss and transfusion rates.[12] Gilbody et al. in a retrospective cohort study of close to 300 patients using 3 grams of topical TXA before closure showed a drop in blood transfusion rate from 19.3 to 2.3% in hip arthroplasty patients and 13.1 to 0% in knee arthroplasty patients.[10]

An estimated 30% reduction in swelling has also been correlated with the use of TXA after total joint arthroplasty and was linked to a better post-operative recovery. No correlation with pain improvement was found.[4,14]

The reduction of blood transfusion has also been correlated of shorter length of stay.[10,13]

The data in our study confirms these pervious reports. The reduction in hemoglobin levels was significantly less in patients treated with TXA in both knee and hip arthroplasty patients. This also led to a significant reduction of packed blood cell transfusions among patients treated with TXA. From 28.8% transfusion rate to 2.9% in knee arthroplasty patients and from 20.2% transfusion rate to 4.0% in hip arthroplasty patients.

Conclusion

Topical intraarticular TXA injections after all primary knee and hip arthroplasty significantly reduce post-operative blood loss anemia without added VTE risk. Its effectiveness and safety have been demonstrated even in patients with cardiorenal diseases, which is why it should be considered in all major orthopedic procedures. This study supports the use of topical TXA.

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