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Alexis Sosa, Ernesto Caceres & Eduardo Dogliani

#### SUMMARY

A study was carried out at a joint reconstruction center in which records from patents who underwent hip and knee prosthetic surgery due to arthrosis were analyzed in 2 periods of time, whose difference lay in the use, as per institutional protocol, of tranexamic acid. Our goal was to assess the hematimetric parameters, complications and the economic impact generated in said center since the introduction of this drug. Information on patronymic variables, type of joint involved, hematimetric parameters, and need of blood product transfusion before surgery was collected before and after operations, and eventual immediate complications directly related to the use of the drug were recorded. Prosthetic replacements, arthroplasties due to fractures and those patients for whom it was not possible to collect the necessary information were excluded from the study.

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## Economic Profile, Effectiveness and Complications of the use of Tranexamic Acidata Joint Reconstruction Center

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#### SUMMARY

A study was carried out at a joint reconstruction center in which records from patents who underwent hip and knee prosthetic surgery due to arthrosis were analyzed in 2 periods of time, whose difference lay in the use, as per institutional protocol, of tranexamic acid. Our *goal was to assess the hematimetric parameters,* complications and the economic impact generated in said center since the introduction of this drug. Information on patronymic variables, type of joint involved, hematimetric parameters, and need of blood product transfusion before collected before surgery was and after operations, and eventual immediate complications directly related to the use of the drug were recorded. Prosthetic replacements, arthroplasties due to fractures and those patients for whom it was not possible to collect the necessary information were excluded from the study.

During the study, 187 procedures were assessed, 98 in hip and 89 in knee, patient mean age was 70 years (range); 61% were males. Tranexamic acid was used in 57% of the operations.

The comparative analysis of groups reveals that none of the patients using tranexamic acid showed severe anemia, while there were 3 patients with severe anemia among those who did not use the drug.

*Out of the 187 patients studied, 21 were transfused postoperatively, all of whom belonged* 

to the group that did not use tranexamic acid. When it comes to complications, 4 patients experienced deep vein thrombosis, 3 of whom belonged to the group in which the drug was not used, although this was not statistically significant.

Since the introduction of tranexamic acid in our center, the use of blood transfusions and blood products has been reduced dramatically without substantial increase of complications and an evident reduction in the associated costs.

#### I. INTRODUCTION

The progressive aging of our population has resulted in an increase of degenerative joint disease. Therefore, the number of prosthetic replacement surgeries has increased considerably, in particular in older patients.1,2.

Primary hip and knee arthroplasties are procedures usually carried out on a daily basis. In general, these surgeries are well-tolerated and have good mid- and long-term results. The loss of perioperative blood requiring allogeneic blood transfusion continues to be a cause of concern. The literature on the topic shows transfusion rates in primary hip and knee surgery to be in the 10% to 38% range. 3,4.

While they have greatly improved as compared to previous years, blood transfusions are not risk-free. Though small, there is still the possibility of disease transmission and reactions to transfusion that may substantially complicate patients' postoperative course. 5,6.

Although health specialists currently tend to restrict the number of transfusions, many times these are unavoidable, in particular in those cases in which preoperative hemoglobin values are not adequate. 7.

Today, it is preferred to customize patient care and minimize allogenic blood transfusions in orthopedic surgery, which is known as "patient blood management." 8.

Thus, the use of different therapeutic options for achieving better clinical results and a reduced dependency on allogenic blood products is considered so as to reduce the risks involved, shorten hospital stays and lower costs per patient. 9, 10.

A number of blood conservation techniques have been developed to reduce blood loss and postoperative transfusion rates, including: controlled hypotension, regional anesthesia, autologous blood transfusion, intraoperative blood recovery, use of erythropoietin, bipolar sealers, and antifibrinolytic agents. 11, 12, 13.

The tranexamic acid is an antifibrinolytic drug that has been shown to be very effective in reducing perioperative bleeding and the subsequent reduction in the need of autologous and/or homologous transfusions. The tranexamic acid has also been shown to be safe, as it does not increase thromboembolic. 14.

In Uruguay, approximately 3,700 knee and hip interventions are carried out in the specialized centers funded by the National Resources Fund. 15.

In view of the high costs of surgery and the eventual cost of blood transfusions, as well as the potential perioperative risks derived from the intervention in itself and the potential risks of patient population suffering from traumatic and/or degenerative hip and knee pathology, the use of disciplinary, medical and evaluation measures has been implemented in order to

reduce the number one cause of preventable death in surgical patients, namely, blood losses.

Extensive research has been done in connection with this drug and its application in orthopedic surgery. In our country, this paper represents a starting point for its assessment.

The aim of this paper is to assess the hematimetric parameters, complications and economic impact generated in a Highly-Specialized Medicine Institute (IMAE) specialized on joint replacement since the introduction of tranexamic acid in our service.

#### II. METHODOLOGY

A cross-sectional, observational, analytic study was carried out at a joint replacement surgery center in the metropolitan area. The medical records of patients who underwent primary prosthetic surgery due to hip and knee arthrosis were analyzed in 2 periods of time, whose difference lies in the use of tranexamic acid as per institutional protocol; Group 1 (patients who did not receive tranexamic acid), and Group 2 (patients who received tranexamic acid). Patronymic variables from each patient (name, identity card number, sex and age) were collected. Preoperative variables were: procedure performed (knee and hip arthroplasty), hemoglobin (g/dl), hematocrit (%), platelets (Nr./mm3), preoperative blood transfusion and its amount in volumes (ml). As for the variables obtained during and after surgery, the following was recorded: use of tranexamic acid during and after surgery and its dose in milligrams, transfusion of blood or blood products during or after surgery and directly related to the intervention performed, immediate complications (pulmonary thromboembolism (PTE), deep vein thrombosis (DVT)), and hemogram 24 hs after surgery (hemoglobin, hematocrit, platelets).

Prosthetic replacements, arthroplasties due to fractures and those patients for whom it was not possible to collect the necessary information were excluded from the study.

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#### III. STATISTICAL ANALYSIS

The main patient characteristics were summarized as percentages, in the case of qualitative variables, and medians and/or means, in the case of quantitative variables. Chi-square test (or Fisher' exact test, where applicable) was used for percentage comparison. A 0.05 significance level was considered in all analytical tests. The statistical processing of data was performed using the SPSS v. 17 software (SPSS Inc., Chicago, Illinois).

#### IV. ETHICAL CONSIDERATIONS

All the information collected in this study is confidential and handled according to the highest ethical standards for epidemiologic research studies. Patient identity was handled only by the physicians who participated in the healthcare process. A dedicated computerized database was created to process the information gathered from patients in a non-personally identifiable way through a code assigned to each patient, only known to study researchers.

#### V. RESULTS

A total of 187 patients, 61% of whom were males and 39% females, with a mean age of 70 years, were analyzed. All prosthesis were implanted due to knee and hip arthrosis, and data on characteristics of studied groups are shown in table 1.

#### Table 1: Main characteristics of the study population

Variable	Ν	%		
Prosthesis				
Hip	98	52.4		
Knee	89	47.6		
Use of tranexamic acid				
No	107	57.2		
Yes	80	42.8		
Dose of tranexamic acid				
500 mg	9	11.3		
1000 mg	45	56.3		
2000 mg	26	32.5		
Preop blood transfusion				
No	185	98.9		
Yes	2	1.1		

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Data on blood transfusion requirements, as well as the number of volumes used during the period of time studied are shown in table 2.

Variable	Ν	%
Blood transfusion		
No	166	88.8
Yes	21	11.2
Blood volumes		
0	166	88.8
1	8	4.3
2	9	4.8
3	2	1.1
4	2	1.1

Table 2: Main Postoperative Data For Study Group.

The hematimetric parameters were classified as b normal hemoglobin values, mild anemia, o moderate anemia, and severe anemia as set forth

by the World Health Organization (WHO). Data obtained are shown in table 3.

Table 3: Postoperative Hematimetric Parameters for Both Study Groups (hemoglobin)

HEMOGRAM	GROUP 1* (N/%)	GROUP 2* (N/%)	p***
Anemia:			
Mild	48 (45)	45 (56)	
Moderate	22 (21)	14 (18)	0.263
Severe	3 (3)	0 (0)	
Normal hemoglobin	33 (31)	21 (26)	

\*GROUP 1: Group of patients who DID NOT receive tranexamic acid \*\*GROUP 2: Group de patients who received tranexamic acid \*\*\*: Pearson's chi-square.

Complications occurred between days 3 and 5 after surgery; 4 patients showed deep vein thrombosis (DVT), while no patient had pulmonary thromboembolism (PTE). Data discriminating these complications according to the use of tranexamic acid are shown in table 4.

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Table A	Com	narison	of (	lomn	lications	Acco	rding	to ·	the	1150	of '	Trane	vamic	Acid	ł
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Complications	Group II <b>(%)</b>	Group I <b>(%)</b>	Р*
DVT	1 (1.3)	3 (2.8)	0.43
TEP	0	0	

Another element analyzed was the relation between the use of tranexamic acid and the need to use blood transfusions after surgery. Without differentiating between hip and knee prosthesis, it was found that out of the 80 Group II procedures, none required blood transfusion after surgery. In contrast, out of the 107 Group I procedures, 21 were transfused, which corresponds to 20% of the total (p: < 0.05).

The cost for both the transfusions needed and the use of tranexamic acid was taken as the basis and goal of this paper. According to our healthcare center, the price for every red cell and/or blood product volume is USD 207, while each 250-milligram ampoule of tranexamic acid costs USD 4.30.

In our study, 21 patients were transfused, with a total of 37 volumes of blood and/or blood products, which amounted to USD 7,700. On the other hand, 101,500 milligrams of the drug were administered for N=80 patients during the same period, with a total cost of USD 1,750. Savings after comparing both groups are estimated to be at 500% thanks to the use of the drug.

## VI. DISCUSSION

Hip and knee prosthetic surgeries are associated to considerable blood loss, which can exceed 1,200 ml, and require postoperative blood transfusion. The literature on the subject shows transfusion rates for primary hip and knee surgery to be between 10% and 38%. (3,4,18).

The risks and costs of allogenic blood transfusion has stimulated the development of strategies to reduce its requirement.

The tranexamic acid is a synthetic antifibrinolytic drug that competitively inhibits the activation of plasminogen into plasmin used to prevent \*: Pearson s chi-square.

bleeding. Several methods are described for the administration of tranexamic acid with the purpose of reducing blood loss in knee prosthesis: intramuscular, oral, intravenous and intraarticular.(19)

Pharmacokinetic studies (20, 21) show that a 20 mg/kg dose of tranexamic acid is adequate for substantially reducing bleeding in hip prosthesis and a therapeutic level can be maintained for about 8 hours after surgery, thus covering the hyperfibrinolysis period, in which 65% of the draining volume has been reported to occur (18, 22).

In our study, the most relevant fact was observed when comparing groups of patients with similar characteristics and administering tranexamic acid: none of the patients needed postoperative blood transfusions as compared to the group of patients who did not receive the drug, which amount to 11% (p < 0.05) - a fact that is in line with international data (16, 17).

In order to quantify blood loss, we based our study in the hematimetric parameters, recording postoperative hemoglobin values for both groups and codifying the information according to international guidelines, such as mild, moderate or severe anemia. Absolute hemoglobin values were higher in group II than in group I. Furthermore, not only was it found that they were higher, but also, in each group (mild, moderate or severe anemia), the percentage of patients within the anemia range was lower to the point where no patients with parameters within the severity range were found in the group that received the drug.

As for costs, tranexamic acid is relatively inexpensive and widely available. Today, hospital cost is about USD100 for every 2000 mg of

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infusion in the USA (in Uruguay it's less than USD50 for every 2000 mg). Although the addition of the drug will increase pharmacy costs, evidence shows that costs for collection room with all the corresponding controls in place, blood bank, laboratory, accommodation, food, and overall hospitalization costs could be reduced. (23, 23, 25, 26, 27, 28, 29)

Slover and Bosco (30) suggested that the cost-effectiveness relation of tranexamic acid in arthroplasty correlated to blood transfusion rates and noted that, when these rates were higher than 25% in any given healthcare facility, the use of this drug reduced them to less than 12%.

Although several factors, such as cost calculation method, market fluctuations, and regional or national variation in medical healthcare expenses, may lead to discrepancies, most of the studies reporting costs provide solid evidence that the use of tranexamic acid is favorable from a cost-effectiveness standpoint.

Another important element to take into account is hospital stays, which have been shown to be shorter and, therefore, are an additional financial benefit derived from the use of tranexamic acid. (23, 29, 31).

In our study, costs where clearly lower in the group that received tranexamic acid, with savings of about 500% when comparing both groups.

When analyzing the impact of the use of tranexamic acid on complications, we did not find an increase in the risk of adverse results in general, nor of thromboembolic events, as these were not statistically significant. These complications have been presented by several physicians as the main reasons for a conservative use of tranexamic acid due to concerns previously published with agents from this category.(25) Since the tranexamic acid inhibits fibrinolysis, safety concerns are based on the fact that interference with the coagulation cascade may promote a procoagulant state and therefore increase the risk of complications, such as

pulmonary embolism, deep vein thrombosis, myocardial infarctions and cerebrovascular events. (25) This is particularly worrying because patients requiring joint arthroplasty have been identified as a particularly vulnerable group for coagulation-based complications as important morbidity and mortality causes. (26)

Another important aspect of the lack of detailed clinical data is reflected in the selective use of tranexamic acid in patients with arterial stents or with a history of thromboembolic events, both considered relative contraindications for the use of tranexamic acid by some physicians. Specifically, in our study we had 3 administration doses of the drug, when the administration protocol provides for only 2 different doses for hip or knee. We are uncertain as to whether this bias was the result of the doctor's negligence or a protocol record failure.

Finally, with regard to tranexamic acid safety, we were only able to study the complications that occurred during hospital stay, which is an inherent limitation of our data source. This could be an underestimation of the real incidence of complications. However, one study showed that more than 90% of complications in unilateral arthroplasties occur within four days of surgery, which suggests that most of the complications should be included in our dataset.(34)

Our study has several limitations. Firstly, our analysis used data from an administrative base and their bias, as well as the lack of information in some cases, such as hemoglobin levels, full medical record, etc., limited the number of patients included in the study.

Another weakness worth mentioning is not including a larger number of patients, as well as not taking into account other healthcare centers that perform these procedures.

Patient follow-up was only carried out for 5 days after surgery, thus excluding other complications that could occur afterwards.

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Future studies in our center must include a 9. H.J. detailed record of doses, strict patient control and continuous follow-up that allows a multivariate analysis of results and complications, with a focus on the specific effectiveness and safety of the tranexamic acid subgroup.

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