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COMPARISON OF HEMOSTASIS WITH TRANEXAMIC ACID IN TOTAL KNEE ARTHROPLASTY

COMPARAÇÃO DA HEMOSTASIA COM ÁCIDO TRANEXÂMICO EM ARTROPLASTIA TOTAL DE JOELHO

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ABSTRACT

Objective: To compare the use of intravenous and topical tranexamic acid (TXA) in unilateral primary total knee arthroplasty (TKA) in relation to blood loss and complications inherent to the medication. Method: Three groups with 14 patients each were constituted, and all of them were operated using the same surgical technique. In Group 1, usual measures for bleeding control were performed. Group 2 patients received TXA topically on the joint surface. In Group 3, intravenous TXA was used. Hemoglobin (HB), hematocrit (HTC), platelets (PLAT), prothrombin time, activated partial thromboplastin time and volume of blood drained observed 24 hours after arthroplasty were compared to the values of tests found before surgery. Results: There was a decrease in the concentration of HB, HTC and PLAT in all groups in relation to the preoperative, however without significant difference. Group 3 had a lower mean volume of drained blood than the other groups, with statistical significance. No adverse effects or thromboembolic events were observed in the groups that received TXA. Conclusion: This study showed superiority in the use of intravenous TXA in decreasing the volume of bleeding, without increasing the risk of thromboembolic events. ***Level of Evidence I, High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals.***

Keywords: Tranexamic Acid. Arthroplasty. Knee. Hemorrhage. Antifibrinolytic Agents. Osteoarthritis, Knee.

RESUMO

Objetivo: Comparar o uso do ácido tranexâmico (ATX) intravenoso e tópico em artroplastia total de joelho primária (ATJ) unilateral em relação à perda sanguínea e complicações inerentes à medicação. Métodos: Três grupos com 14 pacientes cada foram divididos, todos operados utilizando-se a mesma técnica cirúrgica. No Grupo 1, medidas habituais para controle do sangramento foram realizadas. Pacientes do Grupo 2 receberam ATX topicamente na superfície articular. Já no Grupo 3, foi utilizado ATX intravenoso. Hemoglobina (HB), hematócrito (HTC), plaquetas (PLAQ), tempo de protrombina, tempo de tromboplastina parcialmente ativada e volume de sangue drenado observados 24 horas após a artroplastia foram comparados aos valores dos exames encontrados antes da cirurgia. Resultados: Houve queda da concentração de HB, HTC e PLAQ em todos os grupos em relação ao pré-operatório, sem, contudo, diferença significante. O Grupo 3 apresentou menor volume médio de sangue drenado do que os demais grupos, com significância estatística. Não foram observados efeitos adversos ou eventos tromboembólicos nos grupos que receberam o ATX. Conclusão: O presente estudo demonstra superioridade da utilização de ATX intravenoso em diminuir o volume de sangramento, sem aumentar o risco de eventos tromboembólicos. ***Nível de Evidência I, Estudo clínico randomizado de alta qualidade com ou sem diferença estatisticamente significante, mas com intervalos de confiança estreitos.***

Descritores: *Ácido Tranexâmico. Artroplastia. Joelho. Hemorragia. Antifibrinolíticos. Osteoartrite do Joelho.*

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INTRODUCTION

Osteoarthritis (OA) of the knee is one of the most common causes of disability and its prevalence is increasing as older and obese populations grow.[1, 2] More than 50% of people over the age of 65 have radiographic changes in the knee that indicate OA.[1] The risk of developing OA in the knee is due to a multifactorial and complex interaction of constitutional and mechanical factors.[1]

Initial and conservative treatment can be non-pharmacological, including weight loss, aerobic exercise, osteopathic manipulative treatment, or pharmaceutical treatment.[1] In refractory or advanced cases, total knee arthroplasty (TKA) is now a commonly performed surgical procedure.[2,3] TKA allows the patient to move the knee without pain, in addition to maintaining a wide range of daily activities, permitting them to lead a normal life.[2] However, it is associated with large amounts of

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The study was conducted at Hospital da Santa Casa de Misericórdia de Vitória.
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perioperative blood loss and high blood transfusion rates.[4] The blood loss may come from the osteotomized surface of the distal femur and the proximal tibia, from the release of soft tissues and dredging of the marrow cavity.[5] The use of chronic anticoagulant medication and the early rehabilitation of joint function also results in postoperative anemia, which are common concerns for postoperative complications after TKA surgery.[4,5] This finding has led surgeons and researchers to seek pharmacological and mechanical means to avoid this perioperative blood loss as much as possible and to reduce transfusion rates.

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by competitively blocking plasminogen lysine binding sites.[6] Studies have shown that administration of tranexamic acid decreases bleeding after a series of surgical procedures[7-9] including TKA,[5,8,10] without predisposing to thromboembolic complications.[6, 9, 10]

Thus, the present study compared two methods of administering TXA – topical intra-articular and intravenous – with each other and in relation to a control group, with the main objective of evaluating the effectiveness in reducing bleeding and the need for blood transfusion in patients submitted to unilateral primary TKA, in addition to observing the safe use of TXA (secondary objective).

METHOD

Study design, participation criteria and sample size

This is a prospective, randomized study, initiated after approval by the Human Research Ethics Committee of the Higher School of Sciences of Santa Casa de Misericórdia de Vitória, institution where the surgeries were performed, published on *Plataforma Brasil* with the number of opinion 2,449,068. All procedures are in accordance with the 1995 Helsinki declaration. Patients were invited to participate in the research after being duly informed. All signed the Informed Consent Form. The doctor who followed the evolution of patients after the surgical procedures did not participate in them, and was not informed about which line of treatment the patient had been submitted to, so that there was no influence of results at the time of data collection. The procedures were performed in the operating room of a philanthropic hospital in the city of Vitória, state of Espírito Santo, Brazil, which provided access to patient identification data and treatment lines, so that there could be data analysis at the end of the procedure study.

The study included patients older than 55 years in advanced stage of primary knee osteoarthritis according to the criteria of the American College of Rheumatology[11] and with grade IV radiological changes according to the Kellgren and Lawrence classification.[12] Patients with acute occlusive vasculopathy, hypersensitivity to the components of the tranexamic acid formula, no indication for primary total knee arthroplasty, those who abuse alcohol and medications, and who use glucocorticoids or opioids daily were not included.

The total sample size was 42 patients (N = 42) divided equally in three groups (14 in each). The sample size was calculated for comparison among the three groups using the G-Power program, considering the sample size calculation for fixed event analysis, an effect size of 0.5, significance of 5%, power of the 80% test.

In a previously prepared sealed container, 42 envelopes (14 from each group) were inserted, which were randomly selected by a team member on the day of surgery.

Surgical technique and interventions

All patients underwent primary unilateral total knee arthroplasty with preservation of the posterior cruciate ligament (PCL), using the anteromedial parapatellar approach. Lateral release and patellar cutting were not performed in any of the patients.

In Group 1, TKA was performed and only mechanical and electrical blood coagulation methods were used. Such methods were also used in groups 2 and 3. In Group 2, after TKA, patients received 15 mg/kg of TXA in 100 mL of normal saline that was applied topically to the joint surface and left in contact by 10 minutes before the tourniquet is released. Finally, in Group 3, patients were administered intravenously TXA at a dose of 15 mg/kg, 30 minutes before tourniquet deflation.[3] After that, all patients underwent suture in layers, using the same technique, and the installation of a drain by suction (Portovac 4.8 mm). All patients received enoxaparin in their prophylactic dose to prevent thromboembolic events after surgery.

Patients underwent preoperative laboratory tests 30 days or less before surgery and the values of hemoglobin (HB), hematocrit (HTC), platelets (PLAT), prothrombin time and activated partial thromboplastin time were collected. New laboratory tests were collected 24 hours after surgery (hemoglobin, hematocrit, platelets) and these data were compared with preoperative tests. The drains were removed 24 hours after surgery and the volume of blood drained during this period was recorded.

The pre and postoperative moments for the variables HB, HTC and PLAT were compared. We calculated the variation (delta) for these variables and compared the three groups. We also compared the three groups for the following variables: prothrombin time/activity (PT ATV%), prothrombin time/INR (PT INR), activated partial thromboplastin time (APTT) and volume in ml of blood drained in 24 hours. The need for blood transfusion in the postoperative period and thromboembolic complications were also evaluated.

Outcomes

The study presented as its primary outcome the volume of blood drained 24 hours after the TKA was performed. As secondary outcomes, the levels of HB, HTC, PLAT; the need for blood transfusion; the appearance of thromboembolic complications.

Statistical analysis

The results of this work were analyzed using the Paired T-Student tests, ANOVA, Tukey's Multiple Comparison (post hoc). The level of statistical significance was 5%. For statistical analysis, the following software were used: SPSS V20, Minitab 16 and Excel Office 2010.

RESULTS

We observed that there is a mean difference between the pre and postoperative moments for the variables HB, HTC and PLAT in the three groups, (Tables 1, 2 and 3). We did not observe a statistically significant mean difference between the groups for the variation (delta) of HB, HTC and PLAT (Table 4).

Table 1. Comparing preoperative and postoperative moments by group for hemoglobina.

HB		Mean	Median	Standard Deviation	DC	Min	Max	N	CI	P-value
Group 1	Pre	13.18	12.8	1.24	9%	11.4	15.4	14	0.65	<0.001*
	Post	10.36	10.4	1.25	12%	8.1	12.9	14	0.65	
Group 2	Pre	13.48	13.5	0.94	7%	11.9	15.4	14	0.49	<0.001*
	Post	10.99	11.0	1.06	10%	9.0	12.5	14	0.56	
Group 3	Pre	13.03	13.2	1.19	9%	10.8	14.4	14	0.63	<0.001*
	Post	10.35	10.6	1.62	16%	7.7	13.0	14	0.85	

HB, hemoglobin; Pre, preoperative; Post, postoperative; DC, derivation coefficient; Min, minimum; Max, maximum; N, sample size; IC, confidence interval
*Considered statistically significant

Table 2. Comparing preoperative and postoperative moments by group for hematocrit.

HTC		Mean	Median	Standard Deviation	DC	Min	Max	N	CI	P-value
Group 1	Pre	39.54	39.4	3.68	9%	34.4	45.8	14	1.93	<0.001*
	Post	30.54	30.7	3.35	11%	23.9	36.3	14	1.75	
Group 2	Pre	40.44	40.3	2.81	7%	34.7	45.3	14	1.47	<0.001*
	Post	32.71	32.4	3.37	10%	27.3	38.4	14	1.77	
Group 3	Pre	39.65	40.7	3.70	9%	33.0	44.7	14	1.94	<0.001*
	Post	30.81	30.8	4.84	16%	23.2	38.9	14	2.54	

HTC, hematocrit; Pre, preoperative; Post, postoperative; DC, derivation coefficient; Min, minimum; Max, maximum; N, sample size; IC, confidence interval
*Considered statistically significant

Table 3. Comparing preoperative and postoperative moments by group for platelets.

PLAT		Mean	Median	Standard Deviation	DC	Min	Max	N	CI	P-value
Group 1	Pre	230.607	233.000	51.136	22%	129.000	309.000	14	26.786	<0,001*
	Post	171.500	169.000	37.910	22%	110.000	245.000	14	19.858	
Group 2	Pre	214.286	210.500	48.175	22%	156.000	299.000	14	25.235	0,022
	Post	183.357	178.000	31.532	17%	137.000	236.000	14	16.517	
Group 3	Pre	224.407	233.000	38.426	17%	139.000	292.000	14	20.128	<0,001*
	Post	173.071	180.000	28.261	16%	126.000	219.000	14	14.804	

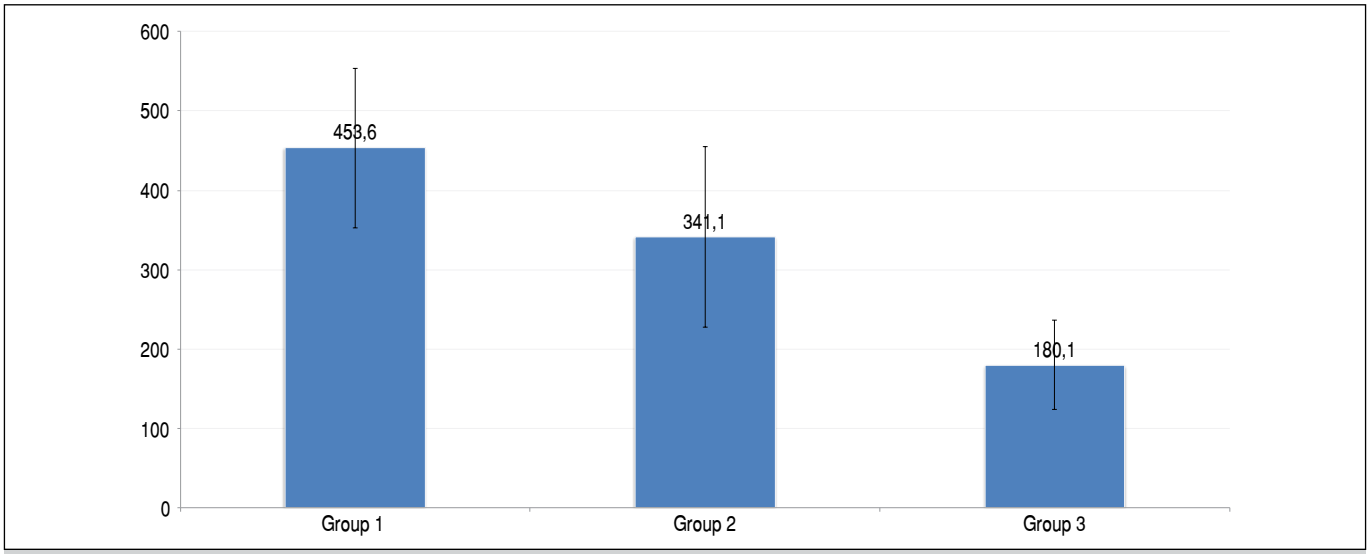
PLAT, platelets; Pre, preoperative; Post, postoperative; DC, derivation coefficient; Min, minimum; Max, maximum; N, sample size; IC, confidence interval
*Considered statistically significant

Table 4. Comparison of the observed variation of HB, HTC and PLAT between the Groups.

Gain		Mean	Median	Standard Deviation	DC	Min	Max	N	CI	P--value
HB	Group 1	-2.82	-2.66	1.11	39%	-4.50	-1.00	14	0.58	0.756
	Group 2	-2.49	-2.25	1.16	47%	-4.70	-1.10	14	0.61	
	Group 3	-2.68	-2.55	1.19	44%	-5.30	-1.00	14	0.62	
HTC	Group 1	-8.99	-8.90	3.71	41%	-16.10	-2.80	14	1.94	0.570
	Group 2	-7.73	-6.50	3.28	42%	-13.40	-4.10	14	1.72	
	Group 3	-8.84	-8.40	3.26	37%	-14.50	-2.70	14	1.71	
PLAT	Group 1	-59.107	-60.500	29.031	49%	-122.500	-17.000	14	15.207	0.104
	Group 2	-30.929	-17.000	44.517	144%	-138.000	8.000	14	23.319	
	Group 3	-51.336	-58.500	29.693	58%	-91.000	23.000	14	15.554	

HB, hemoglobin; HTC, hematocrit; PLAT, platelets; Pre, preoperative; Post, postoperative; DC, derivation coefficient; Min, minimum; Max, maximum; N, sample size; IC, confidence interval

The comparison of the volume of blood drained (Graph 1) showed a statistical difference between the groups (Table 5). We observed that this difference was made between Group 1 compared to Group 3 (Table 6).



Graph 1. Graph comparing the volume (ml) of blood drained in 24 hours.

Table 5. Comparison of Groups for PT, APTT and Drained Blood (ml).

Groups		Mean	Median	Standard Deviation	DC	Min	Max	N	CI	P-value
PT (ATV%)	Group 1	89.3	88.0	7.3	8%	78.5	100.0	14	3.8	0.516
	Group 2	92.0	93.1	10.9	12%	77.6	115.5	14	5.7	
	Group 3	92.9	95.1	7.3	8%	76.7	100.0	14	3.8	
PT (INR)	Group 1	1.056	1.065	0.068	6%	0.880	1.150	14	0.036	0.377
	Group 2	1.058	1.030	0.082	8%	0.940	1.260	13	0.045	
	Group 3	1.051	1.055	0.052	5%	1.000	1.190	14	0.027	
APTT	Group 1	1.006	1.000	0.121	12%	0.820	1.280	14	0.063	0.288
	Group 2	1.054	1.010	0.077	7%	1.000	1.250	14	0.040	
	Group 3	1.008	1.015	0.063	6%	0.850	1.072	14	0.033	
Drained Blood	Group 1	453.6	475.0	191.9	42%	200.0	710.0	14	100.5	0.001*
	Group 2	341.1	332.5	216.7	64%	100.0	890.0	14	113.5	
	Group 3	180.1	165.0	106.5	59%	55.0	400.0	14	55.8	

PT (ATV%), prothrombin time/activity; PT (INR), prothrombin time/international normalized ratio; APTT, activated partial thromboplastin time; DC, derivation coefficient; Min, minimum; Max, maximum; N, sample size; IC, confidence interval
*Considered statistically significant

Table 6. P-values for blood volume drained (ml) from Table 5.

		Group 1	Group 2
Drained Blood	Group 2	0,229	
	Group 3	0,001*	0,055

*Considered statistically significant

We did not observe any difference among groups for the variables prothrombin time/activity (PT ATV%), prothrombin time/INR (PT INR), activated partial thromboplastin time (APTT).
One patient in the control group had pulmonary thromboembolism. Only one patient in group 3 required blood transfusion in the postoperative period. There were no surgical complications, death or other complications during the experiment.

DISCUSSION

TKA is recognized as a successful procedure, increasingly performed in orthopedics, since the population has aged and needs a better quality of life. However, TKA has some complications that still need a definitive resolution, including intra and postoperative bleeding with consequent hemodynamic[8] and infectious disorders.[13,14]
The use of a tourniquet is capable of considerably diminishing intraoperative bleeding,[15] contributing to decrease hemodynamic effects as well as allowing for cleaner surgery, even facilitating the cementation of implants.[15] However, when it is used, most bleeding in TKA occurs after its release,[16] with no significant difference between its early (before skin suture) or late (after dressing the compressive dressing).[17]
Therefore, the use of pharmacological strategies aimed at reducing bleeding, especially after the release of ischemia, has been both gaining adherents and being the target of several studies. Among these strategies, the use of TXA[2,8,13,18] draws attention.
In addition to elective surgery, TXA is also used successfully, reducing the need for transfusions and death from hypovolemic shock in trauma victims, without increasing the risk of thromboembolic events[9].
The way in which TXA has been administered varies, however[2,5,7-10,13,18]. The present study sought to compare two different strategies for using TXA: topical intra-articular application and intravenous use.
Our results demonstrated that both topical and intravenous use of TXA is safe, since no adverse effects or increased thromboembolic events were observed when compared with the control group. Besides, these results are in line with other studies.[2,5,8,10,13,18]
Our study also demonstrated that the control group had greater blood loss when compared with the groups that received TXA, which is explained by the antifibrinolytic effect of the drug,[6] as well as was verified in other studies[2,5,8,10,13,18] who used TXA in knee arthroplasties in different doses and forms of application.
The study by Aggarwal et al.[2] observed a lower volume of bleeding when topical rather than intravenous TXA was used in bilateral primary knee arthroplasties performed simultaneously.
In our comparison, we evidenced that the intravenous use of TXA was more effective in reducing bleeding in the postoperative period than topical application, with a significant result. The volume of blood drained in 24 hours was, on average, 341.1 ml for group 2 and 180.1 ml for group 3. However, there was no statistically significant decrease in the loss of hemoglobin and hematocrit between the groups. A similar result was also observed in a study alike ours, even though the doses of TXA administered varied.[18] Even so, taking into account the possible complications of hematoma formation, such as infections,[13,14] delayed healing[19] and increased postoperative pain,[14,20] we can infer the advantage of intravenous use of TXA

CONCLUSION

Our study showed superiority in the use of intravenous tranexamic acid in relation to the topical use of tranexamic acid and the control group, in view of the lower volume of blood drained. The use of tranexamic acid proved to be safe, once no possible adverse reactions from its use or thromboembolic events were observed in patients in the groups in which it was administered.

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