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Article *in* The Journal of Knee Surgery · July 2021

DOI: 10.1055/s-0041-1731455

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Benefits of Tranexamic Acid in Total Knee Arthroplasty: A Classification and Regression Tree Analysis in Function of Instrumentation, BMI, and Gender

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J Knee Surg

Abstract

Tranexamic acid (TXA) is an antifibrinolytic drug that reduces blood loss in patients that undergo Total knee arthroplasty (TKA). Few studies compare its effect on conventional instrumentation (CI) versus patient-specific instrumentation (PSI). The main objective of this study was to understand analytically how TXA usage in both instrumentations influenced blood loss in TKA differently and see if the differences seen could be explained by the patient's body mass index (BMI) and gender. This nonrandomized retrospective study sample consisted of 688 TKA procedures performed on patients who had symptomatic arthrosis resistant to conservative treatment. Descriptive analysis was used to evaluate blood loss using hemoglobin (Hb) mean values and mean variation (%). The Classification and Regression Tree (CRT) method was applied to understand how the independent variables affected the dependent variable. Comparing patients submitted to the same instrumentation, where some received TXA and others did not, patients that received TXA had lower blood loss. Comparing patients who underwent TKA with different instrumentations and without the use of TXA, it was found that patients who underwent TKA with PSI had lower blood loss than those who underwent TKA with CI. However, when these same instruments were compared again, but associated with the use of TXA, the opposite was true with patients undergoing TKA with PSI showing greater blood loss than patients undergoing TKA with CI. TXA usage in TKA is significantly beneficial in minimizing blood loss and regardless of instrumentation. When using TXA, the lowest blood loss was obtained in patients with higher BMI and submitted to TKA with CI. This is most likely explained by the synergistic antifibrotic effect of TXA with adipokines, such as plasminogen activator inhibitor-1 (PAI-1), found in the femoral bone marrow which is perforated using CI. If, however, TXA wasn't used, the lowest blood loss was obtained in patients submitted to TKA with PSI.

Keywords
- total knee replacement
- tranexamic acid
- instrumentation
- surgical blood loss
- plasminogen activator inhibitors

received
December 30, 2020
accepted after revision
May 1, 2021

DOI https://doi.org/10.1055/s-0041-1731455.
ISSN 1538-8506.

Total knee arthroplasty (TKA) is an orthopaedic surgery procedure performed worldwide, with excellent results in reducing pain and restoring functionality in patients with end-stage knee osteoarthritis.[1–11]

Conventional instrumentation (CI), the standard option for TKA, uses intramedullary and/or extramedullary alignment systems that rely too much on visual references which can lead even an experienced surgeon to produce undesired postoperative axes.[5,8,10] These devices not only complicate the workflow and prolong surgery time but also can increase blood loss and the risk of fat embolism, as they are more invasive.[5,10]

Patient-specific instrumentation (PSI) emerged in the last two decades as an alternative to CI, aiming to improve accuracy and cost effectiveness in daily use, as well as reduce operating times, and blood loss caused by TKA.[1,3,5,8,12,13]

TKA frequently presents perioperative blood losses, due to soft-tissue dissection and bone cuts,[14–18] estimated between 1,500 and 2,000 mL, with a predictable decrease of 3 g/dL of hemoglobin (Hb) for every 1,000 mL of blood loss.[12,19] Blood loss increases morbidity, mortality and dissatisfaction of patients but it also prolongs hospital admission and increases costs.[15,16]

Blood transfusions have an undeniable value but they also pose some risks such as infections, immunological reactions, and even death.[6,14,15,19–22]

The trauma caused by surgery releases from the vascular endothelium tissue plasminogen activator (TPA), the enzyme responsible for converting plasminogen into plasmin, thereby activating fibrinolysis.[21] Tranexamic acid (TXA) is an antifibrinolytic synthetic drug that limits blood loss by inhibiting this conversion (►**Fig. 1**), thus delaying the degradation of the fibrin clot (fibrinolysis), reducing blood loss, and the need for transfusions.[9,15,16,19,20,22–25]

Current literature supports the use of TXA in patients undergoing TKA, as reducing blood loss will minimize complications and hospital costs.[14,15,17,21,23–28] Despite some initial fear that it might induce thrombotic events, the widespread use of TXA has confirmed its safety, corroborated by many studies, although no consensus has been reached on doses or forms of administration in TKA.[16,24–27]

Recent studies have concluded that individual characteristics influence TXA action on TKA differently, presenting worse results in terms of blood loss in patients with lower body mass index (BMI).[18,29]

As current evidence suggests that both PSI and TXA individually reduce blood loss in TKA, it would be assumed that, when combined, these would result in the least possible blood loss. However, this was not the case in our clinical practice which showed mixed results.

This study is innovative because its main objective is to understand analytically how the use of different instrumentations, such as CI or PSI, when combined with TXA influences blood loss in TKA differently, also taking into account BMI and gender, and using a Classification and Regression Tree (CRT) analysis for that purpose.

Since TKA is such a widespread orthopaedic procedure, it is important to provide surgeons with reliable information that allows them, depending on individual patient characteristics, such as BMI and gender, to choose the instrumentation that achieves the best results with the least blood loss.

Methods

Study Design

This nonrandomized retrospective study (evidence level III) was implemented using data collected from the Hospital

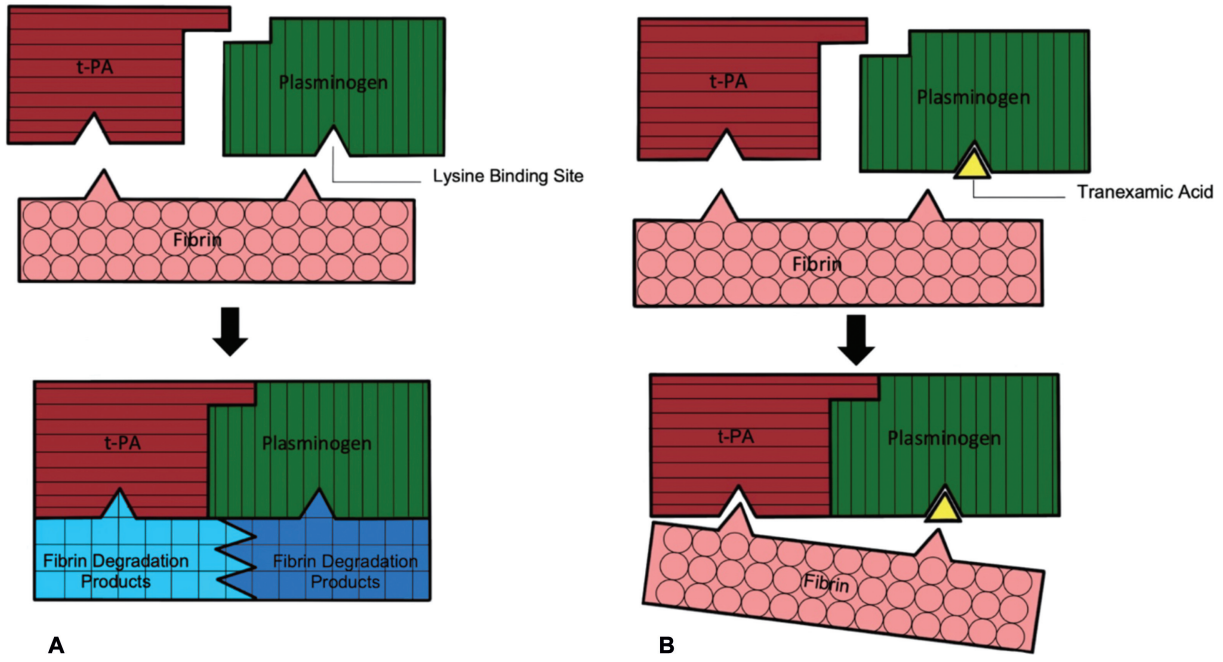

Fig. 1 Mechanism of action of tranexamic acid (TXA). (**A**) Representation of the physiologic degradation of fibrin clots occurring naturally in our bodies and promoted by the binding of tissue plasminogen (t-PA) and plasminogen to fibrin. (**B**) Representation of the action mechanism of TXA, which protects the fibrin clot by preventing the binding of plasminogen with fibrin, hence reducing the bleeding.

Particular do Algarve (Gambelas) database which covers all the patients who underwent TKA between 2011 and 2020. The study was approved by the medical ethical committee at the hospital. Patients and clinicians allowed the usage of their data for this study. The dependent variables of this study were Hb and Variation of Hb (%) and the independent variables were age, gender, BMI, TXA, and instrumentation.

Inclusion and Exclusion Criteria

Sample size consisted of all patients who had symptomatic arthrosis resistant to conservative treatment (convenience sampling) and underwent TKA at Hospital Particular do Algarve (Gambelas) between the years 2011 and 2020, amounting to 688 TKA procedures. After the first year of testing PSI in TKA, 2011, it became the standard procedure and therefore all patients, regardless of the severity of joint deformity, were allocated to this group by default. However, whenever technical constraints (inability to perform MRI or poor fitting of the cutting blocks) or logistical constraints (lack of time to do the cutting blocks or delays) occurred, these patients were automatically switched to the CI group.

As to TXA use, this study sample was divided into a group which used TXA and a group that did not. These groups were separated temporally by the implementation of its use in the hospital protocols for TKA in 2016. Patients' distribution between these two groups can be better seen in ►**Fig. 2**.

Procedures

Surgeries were performed with a tourniquet inflated at the beginning of the surgery and released after dressing the sutured wound. All operations were done by conventional medial parapatellar approach. Patients received a cemented implant without patella replacement and with preservation of the posterior cruciate ligament. If preservation of the posterior cruciate ligament was not possible, an ultracongruent implant was used. The capsule was closed with continuous suture without drain usage. No cement or femoral plug was ever used in the patients submitted to CI. All patients were given 1 g of TXA intraoperatively 15 minutes before tourniquet release. A peri- and intra-articular instillation of ropivacaine was performed, and the knee was in flexion for 15 minutes after tourniquet release. Chemical thromboprophylaxis with enoxaparin 40-mg once daily for the first 30 postoperative days was used for each patient. Transfusion triggers were Hb <7 and <8 g/dL in patients with symptomatic anemia and cardiovascular disease, respectively. All surgeries were performed using prostheses from the manufacturer Smith & Nephew. Between 2011 and 2013, the TC Plus Primary prosthesis was used which the manufacturer replaced in 2013 with the LEGION prosthesis, which was used until the end of this study. In the authors' opinion, this did not impact the outcomes, since the rationale and design behind the two prostheses is very similar. All patients were operated by the same team with constant presence of the senior surgeon.

Statistical Analysis

The database was anonymized before performing descriptive and inferential statistics analysis using the SPSS 26 software (IBM Inc., Armonk, NY). As for descriptive statistics, mean, standard deviation and frequencies (absolute and relative) were obtained depending on what variable was being studied. The *t*-test for independent samples was applied in the continuous numeric variables and Qui-square tests in the dichotomic nominal variables, considering the variation of Hb as the variable being tested. To understand how all the independent variables interacted with the dependent variable, a multivariate analysis was done using the CRT which provided a decision tree ($p < 0.05$) based on the variation of Hb (%).

Results

A total of 471 (68.5%) TKA was performed in female patients and 217 (31.5%) TKA in male patients, aged 48 to 92 and 49 to 90 years, respectively. No statistical difference ($p = 0.708$) was found between the mean ages of the female (70.1 ± 7.9) and male (70.3 ± 7.8) groups.

BMI was separated into three groups: (1) BMI $< 25\ kg/m^2$, (2) BMI $= 25$ to $30\ kg/m^2$, and (3) BMI $> 30\ kg/m^2$. Group 1 presented an average of 23.3 (± 2.0) in females and an average of 23.6 (± 1.3) in males. Group 2 showed an average of 27.5 (± 1.3) in females and an average of 27.7 (± 1.4) in 75 males. Group 3 presented an average of 34.3 (± 3.6) in

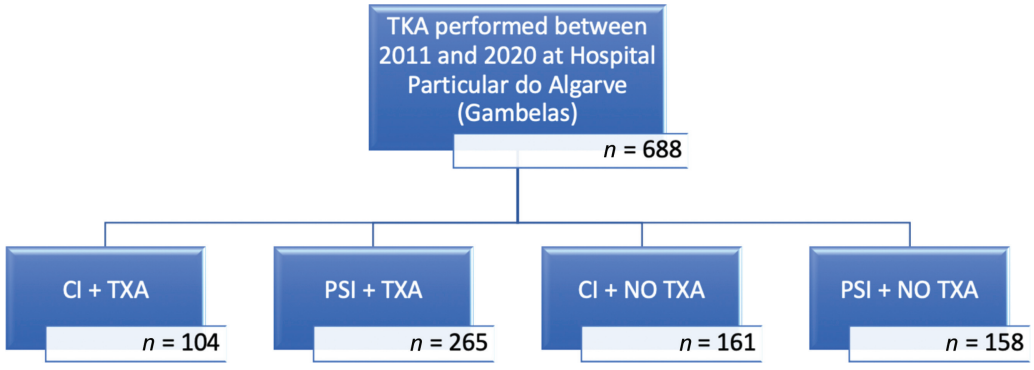

Fig. 2 Visual representation of the distribution of patients across the four groups: CI + TXA, PSI + TXA, CI + no TXA and PSI + no TXA. CI, conventional instrumentation; PSI, patient-specific instrumentation; TKA, total knee arthroplasty; TXA, tranexamic acid.

females and an average of 32.8 ($\pm$2.7) in 52 males. Only group 3 showed a significant difference between genders ($p < 0.05$).

Regarding instrumentation, 189 (71.1%) female patients and 77 (28.9%) male patients were submitted to CI, while 282 (66.8%) female patients and 140 (33.2%) male patients were submitted to PSI. There was no statistical significance between the four groups ($p = 0.245$).

In the female group, 218 (68.8%) patients didn't use TXA, while 252 (68.1%) did. In the male group, 99 (31.2%) didn't use TXA, while 118 (31.9%) did. TXA use wasn't significantly different between the four groups ($p = 0.852$).

The Hb values of preoperative female patients presented a mean of 13.3 g/dL ($\pm$1.2), while the Hb values of preoperative male patients presented a mean of 14.7 g/dL ($\pm$1.5), with a strong statistical significance between genders ($p < 0.001$).

Postsurgery Hb values of female patients had a mean of 11.1 g/dL ($\pm$1.3), while male patients had a mean of 12.1 g/dL ($\pm$1.6) with a strong statistical significance between the genders ($p < 0.001$).

The mean variation of Hb (%) pre- and postsurgery was 17.0% ($\pm$7.0%) in the female group and 17.4% ($\pm$7.6%) in the male group, without statistical significance ($p = 0.418$). All of the above information can be found in ►**Table 1**.

Mean differences between preoperative and 24 hours of postoperative Hb (g/dL) were calculated in the four possible groups. All the above information is shown in ►**Table 1**.

When comparing CI (2.66 ± 1.1) against PSI (2.61 ± 1.0) without using TXA, no statistical significance was observed between groups ($p = 0.696$). However, when comparing CI (1.96 ± 0.9) against PSI (2.19 ± 1.0) with TXA usage, there was a statistical significance between groups ($p < 0.05$) with CI being the more advantageous instrumentation.

In the CI groups, using TXA resulted in smaller blood loss than not using it (1.96 ± 0.9 and 2.66 ± 1.1, respectively), and in the PSI groups, the use of TXA also resulted in smaller blood loss than not using it (2.19 ± 1.0 and 2.61 ± 1.0, respectively). There was a significant advantage in using TXA for both comparisons ($p < 0.001$).

The above information can be found in ►**Table 2**. ►**Table 3** was built as an attempt to make sense of these values, displaying the mean variation of Hb (%), broken down by instrumentation, TXA, gender and BMI. To further understand these values, a multivariate analysis was then performed using the CRT method, which provided a decision tree discriminating the dependent variation of Hb (%) presented in ►**Fig. 3**.

Regarding the CRT, each time two variables were compared the variable with a smaller Hb variation (better

Table 1 Sample characteristics

	Female	Male	*p*-Value
	68.5% (*n* = 471)	**31.5% (*n* = 217)**	
Age (y) Mean (SD[a]), n	70.1 ($\pm$7.9), 464	70.3 ($\pm$7.8), 214	0.708
BMI[b] (kg/m^2) Mean (SD[a])			
<25	23.3 ($\pm$2.0), 57	23.6 ($\pm$1.3), 23	0.319
25–30	27.5 ($\pm$1.3), 129	27.7 ($\pm$1.4), 75	0.769
>30	34.3 ($\pm$3.6), 147	32.8 ($\pm$2.7), 52	<0.05
Instrumentation, *n* (%)			
CI[c]	189 (71.1)	77 (28.9)	0.245
PSI[d]	282 (66.8)	140 (33.2)	
TXA[e], *n* (%)			
Without	218 (68.8)	99 (31.2)	0.852
With	252 (68.1)	118 (31.9)	
Hemoglobin Mean (SD[a]), *n*			
Presurgery	13.3 ($\pm$1.2), 455	14.7 ($\pm$1.5), 212	<0.001
24h postsurgery	11.1 ($\pm$1.3), 466	12.1 ($\pm$1.6), 213	<0.001
Hemoglobin variation (%)	17.0 ($\pm$7.0), 433	17.4 ($\pm$7.6), 210	0.418

Abbreviations: BMI, body mass index; CI, conventional instrumentation; PSI, patient-specific instrumentation; SD, standard deviation; TXA, tranexamic acid.
[a]Standard deviation.
[b]Body mass index.
[c]Conventional instrumentation.
[d]Patient-specific instrumentation.
[e]Tranexamic acid.

Table 2 Mean Hb difference (g/dL) using CI or PSI with and without TXA

	CI[a]	PSI[b]	*p*-Value
Without TXA[c]	2.66 (±1.1)	2.61 (±1.0)	0.696
With TXA[c]	1.96 (±0.9)	2.19 (±1.0)	0.048
p-value	<0.001	<0.001	

Abbreviations: CI, conventional instrumentation; Hb, hemoglobin; PSI, patient-specific instrumentation; TXA, tranexamic acid.
[a]Conventional instrumentation.
[b]Patient-specific instrumentation.
[c]Tranexamic acid.

Table 3 Mean Variation of Hb (%) discriminated by Instrumentation, TXA, gender, and BMI

		Female		Male	
		CI[c]	PSI[d]	CI[c]	PSI[d]
	BMI[b] (kg/m^2)	Mean (±SD[e])	Mean (±SD[e])	Mean (±SD[e])	Mean (±SD[e])
Without TXA[a]	<25	17.6 (±7.4)	19.0 (±5.0)	20.2 (±13.2)	16.9 (±8.1)
	25–30	20.1 (±7.1)	17.9 (±6.3)	17.9 (±6.3)	17.5 (±6.9)
	>30	19.9 (±8.5)	18.4 (±6.2)	19.1 (±8.5)	19.8 (±8.1)
With TXA[a]	<25	12.7 (±6.2)	18.5 (±5.7)	22.2 (-)	17.1 (±5.8)
	25–30	15.1 (±5.3)	15.0 (±6.4)	14.9 (±7.4)	16.5 (±6.4)
	>30	13.2 (±5.4)	15.00 (±6.4)	15.9 (±5.9)	15.7 (±8.9)

Abbreviations: BMI, body mass index; CI, conventional instrumentation; Hb, hemoglobin; PSI, patient-specific instrumentation; SD, standard deviation; TXA, tranexamic acid.
[a]Tranexamic acid.
[b]Body mass index.
[c]Conventional instrumentation.
[d]Patient-specific instrumentation.
[e]Standard deviation.

outcome) was highlighted in green and the one with a higher Hb variation (worse outcome) was highlighted in orange.

The first independent variable which opens two branches is the usage or not of TXA.

Looking at the left side of the tree (without TXA), the second most important variable is instrumentation. For the CI group, the next variable to cause a split is gender. For the PSI group, the next variable to cause a split is BMI, with patients with a BMI < 25 kg/m^2 on one side and patients with a BMI > 25 kg/m^2 on the other side. Drawing more conclusions from this point on is difficult.

Looking at the right side of the tree (with TXA), the second most important variable is BMI, with patients with BMI > 25 kg/m^2 on one side and patients with BMI < 25 kg/m^2 on the other side. Patients with a BMI > 25 kg/m^2 are further split by gender first and instrumentation afterward, whereas the

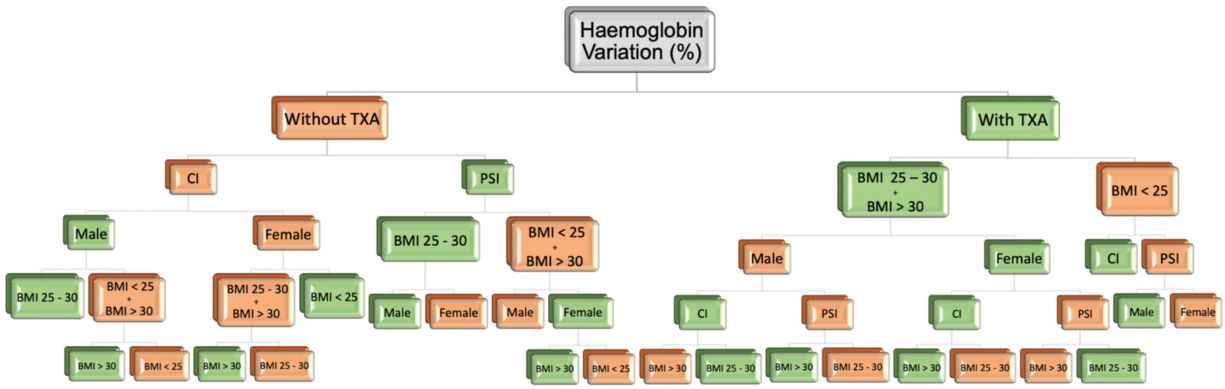

Fig. 3 Representation of the Classification and Regression Tree (CRT). Hb variation (%) was the dependent variable, while TXA, instrumentation, gender, and BMI were the independent variables. The different colors express the results of the various direct comparisons, always made between 2 branches of CRT. The green boxes represent the lowest blood loss, and the orange boxes the highest blood loss resulting from that comparison, expressed by Hb variation (%). Global risk was 46,922 (±3,153). BMI, body mass index; CRT, the Classification and Regression Tree; Hb, hemoglobin; TXA, tranexamic acid.

patients with BMI $< 25\,kg/m^2$ are split by instrumentation first and gender later. Still on the right side of the tree, each time CI is compared against PSI, it becomes clear that the CI group always presents a smaller variation of Hb (%), while on the left side of the tree, we see the opposite. From this point on, it is hard to draw more conclusions.

Discussion

Regarding the use of TXA in TKA, this study concluded that it was the biggest determining factor for blood loss, with significant blood loss reduction for the groups which used TXA compared with the groups which did not (►**Table 2**; ►**Fig. 3**). Many studies found in the literature also support its use for the same purpose.[14,15,17,21,23–28]

As for the instrumentation used, overall PSI showed lower blood loss in the group not using TXA. Kizaki et al reported similar findings in a 2019 meta-analysis, also giving the advantage to PSI over CI in terms of blood loss but without statistical significance.[10] However, when comparing CI with PSI in the groups that used TXA, CI was the clear winner in every single comparison (►**Fig. 3**). In other words, the benefit of using PSI rather than CI, combined with TXA usage to reduce blood loss, appeared to be lost, providing clarification on the investigation goal set out by the authors. The CRT (►**Fig. 3**) only confirmed what ►**Table 2** had previously implied. This finding is of paramount importance, since very few studies have so far compared blood loss, taking into account TXA usage or not in both different instrumentations used in TKA.

Regarding BMI, this study suggests that, in general, patients with higher BMI had lower blood loss. This variable is even more relevant for blood loss in the patient's group in which TXA associated with CI was used. This is in contrast with patients who did not use TXA where instrumentation played a greater role than BMI in blood loss.

These last two findings led the authors to question whether the answers could be found in the adipocytes.

Both Viegas et al and Meng et al in studies from 2020 and 2018, respectively, demonstrated that using TXA in patients with higher BMI would result in smaller blood losses when compared with TXA usage in patients with smaller BMIs.[18,30] Higher BMI is associated with higher values of plasminogen activator inhibitor-1 (PAI-1),[30–33] a protein synthesized by the endothelium, liver, and adipocytes.[31,33,34] PAI-1 prevents the conversion of plasminogen to plasmin and subsequently produces antifibrinolytic effects.[30–32,34] Since it is an inhibitor of TPA, and since both TXA and PAI-1 are important inhibitors of fibrinolysis, their synergism can result in a greater antifibrinolytic effect.[30]

The main surgical difference between CI and PSI is that the former implies marrow perforation,[3,5,8,10] which alone could possibly explain the superior results of CI when combined with the use of TXA in terms of blood loss. Not only the highly invasive surgery has been shown to promote a hypercoagulable state,[21] which results in lower blood loss, but also there is PAI-1 production at the site of tissue injury resulting from inflammation associated with the surgical incision.[35,36]

Furthermore, adipocytes—now recognized as a major endocrine organ—[37] are greatly represented in bone marrow, accounting for up to 70% of bone marrow volume and representing over 10% of total adipose tissue in healthy adults.[38–40] Bastelica et al, in a 2002 study, found that stromal cells, which include bone marrow cells, were the main source of PAI-1 production.[41] The importance given to adipokines, and in particular to PAI-1, has been growing in recent years with some authors predicting its future use in monitoring and treating conditions.[42] This alone may justify the better results of CI associated with TXA presented in this study. It is also important to have into account that no cement or femoral plug was used in patients submitted to CI. Had it been used, the results might have been different, since bone marrow and adipokine exposure to TXA would have possibly been lower, a cause of increase blood loss postulated by the authors but not proven in this study. Additional studies should be conducted.

Finally, as for gender, the authors believe that the differences observed may be a consequence of having a sample with more female patients (68.5%), particularly evident in BMI $> 30\,kg/m^2$ groups, the female sample being three times bigger than the male one. This adds to the fact that, according to this study's results, TXA has overall more pronounced effects on blood loss in patients with higher BMI. However, the possibility that the Hb variation (%) observed in this study results has another unknown explanation that cannot be ruled out either.

Limitations

One limitation of this study concerns ►**Table 2**. If instead of comparing Hb mean differences (g/dL) between groups, Hb variation (%) was compared, it would no longer be possible to grasp the statistical significance between CI and PSI associated with TXA usage ($p = 0.67$ instead of < 0.05).

Another limitation was the selection of patients making up this study sample which was obtained by convenience and does not guarantee a good representation of the population. Therefore, some caution is needed when inferring conclusions.

A final limitation of this study was the decision to use or not TXA and which instrumentation to use which was not randomized.

Conclusion

This study demonstrates that TXA is always significantly beneficial in TKA, regardless of the instrumentation used, and so the authors recommend always using TXA to minimize blood loss.

If the surgeon chooses to use TXA, he will obtain the lowest blood loss in patients with a higher BMI and submitted to TKA with CI. This was the main finding of the study, most likely explained by the synergistic antifibrotic effect of TXA with adipokines, such as PAI-1 found in the bone marrow, and which are more likely to contact with the TXA in TKA with CI, since this surgical technique implies femoral medullar perforation.

If, however, the surgeon does not use the TXA, in light of the findings obtained in this study, the authors recommend that the surgeon chooses PSI to achieve the lowest possible blood loss, a finding also well supported in literature.

Conflict of Interest
None declared.

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