

Prospective Study on the Impact of the Use of Human Fibrin Sealant free of Clot-Stabilizing Agents in Total Knee Arthroplasty*

Estudo prospectivo sobre o impacto do uso do selante de fibrina humano livre de agentes estabilizadores de coágulo na artroplastia total de joelho

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Abstract

Objective The present study aimed to evaluate the results of the intraoperative topical use of a human fibrin sealant free of clot-stabilizing agents in total knee arthroplasties (TKAs), looking for differences between groups regarding blood loss, transfusion requirement, length of hospital stay, pain perception, range of motion (ROM), and incidence of complications.

Methods We have analyzed prospectively an intervention group with 32 patients (Sealant) and a control group with 31 patients (Control) with symptomatic knee osteoarthritis who underwent TKA.


Results The results were similar between the groups regarding visible blood loss in the drain in 24 hours (Control, 276.5 mL \pm 46.24 versus Sealant, 365.9 mL \pm 45.73), total blood loss in 24 hours (Control, 930 mL \pm 78 versus Sealant, 890 mL \pm 67) and in 60 hours after surgery (Control, 1,250 mL \pm 120 versus Sealant, 1,190 mL \pm 96), blood transfusion requirement (which occurred only in 1 control patient), length of hospital days stay (Control, 5.61 \pm 0.50 versus Sealant, 4.81 \pm 0.36), postoperative pain, and ROM. Sealant use was not related to wound healing complications, to infection, or to deep venous thrombosis.

Conclusion We have concluded that the hemostatic agent composed of human fibrin was not effective in reducing bleeding volume and blood transfusion requirement, nor it interfered with hospital length of stay, pain perception, and ROM. Its use was not related to any complications.

Keywords

- arthroplasty, replacement, knee
- osteoarthritis
- blood loss
- fibrin sealant

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Resumo

Objetivo O objetivo do presente estudo foi avaliar os resultados do uso tópico intraoperatório do selante de fibrina humano livre de agentes estabilizadores de coágulo em pacientes com osteoartrite (OA) submetidos a artroplastia total de joelho (ATJ), buscando diferenças entre os grupos em relação à perda sanguínea, à necessidade transfusional, ao tempo de internação hospitalar, à percepção de dor, à amplitude de movimento e à incidência de complicações.

Métodos Foram analisados prospectivamente um grupo de intervenção (Selante) com 32 pacientes e um grupo controle (Controle) com 31 pacientes, com OA sintomática dos joelhos, submetidos a ATJ.

Resultados Os resultados foram semelhantes entre os grupos, em relação à perda sanguínea visível no dreno em 24 horas (Controle 276,5 mL \pm 46,24 *versus* Selante 365,9 mL \pm 45,73), à perda sanguínea total em 24 horas (Controle 930 mL \pm 78 *versus* Selante 890 mL \pm 67) e em 60 horas de pós-operatório (Controle 1.250 mL \pm 120 *versus* Selante 1.190 mL \pm 96), à necessidade de hemotransfusão (ocorreu em apenas 1 controle), ao tempo de dias na permanência hospitalar (Controle 5,61 \pm 0,50 [$n = 31$] *versus* Selante 4,81 \pm 0,36), dor pós-operatória e amplitude de movimento. O uso do agente selante de fibrina não se relacionou à ocorrência de complicações da cicatrização de ferida, de infecção, ou de trombose venosa profunda.

Palavras-chave

- ▶ artroplastia de joelho
- ▶ osteoartrite
- ▶ perda sanguínea
- ▶ selante de fibrina

Conclusão Concluímos que o agente hemostático de fibrina humana não foi eficaz em reduzir o volume de sangramento nem a necessidade de hemotransfusão, ou em interferir no tempo de internação hospitalar, na percepção de dor ou na amplitude de movimento. Seu uso não se relacionou a nenhuma complicação.

Introduction

Knee osteoarthritis (OA) involves cartilage degeneration, synovial inflammation, and subchondral bone thickening, resulting in pain and functional limitation. Total knee arthroplasty (TKA) is one of the treatment options for the final stages of the disease, reducing symptoms and restoring joint function. Implant design and fixation have progressively improved, leading to an increased survival and functionality. However, blood loss related to this procedure is still a concern that needs to be investigated and addressed.¹⁻⁴

Blood loss control and prevention strategies include the use of pneumatic tourniquets, hypotensive anesthesia, blood transfusions, and pharmacological agents; the latter, however, may be related to complications inherent to their use.^{5,6}

Several studies using topical fibrin sealants, such as Quixil (Omrix Biopharmaceuticals, New York City, NY, USA) and Floseal (Baxter International, Deerfield, IL, USA), have shown their efficacy in reducing visible blood loss, total bleeding, and blood transfusion rates in TKAs.⁷⁻¹¹ However, these drugs may be related to thromboembolic and allergic complications due to the presence of clot-stabilizing agents in their formulas, such as tranexamic acid (TA) and aprotinin.¹² A new generation of fibrin sealants (Evicel, Johnson & Johnson, New Brunswick, NJ, USA), containing no such agents, was then developed.¹³

The present study aimed to evaluate the intraoperative use of a topical human fibrin sealant free of clot stabilizers in TKA and its influence on blood loss, on blood transfusion requirements, on the length of hospital stay, on pain percep-

tion, on the range of motion (ROM), and on the incidence of complications.

Methods

The study population consisted of 64 patients submitted to TKA for primary knee OA treatment between September 2015 and April 2017.

Patients > 55 years old with at least 90° range of motion (ROM), with no significant angular deformities, and presenting OA radiographic changes graded 4 or 5 according to the Ahlback system were included in the study after signing the informed consent form. Complying with ethical standards, the present study was approved by the Institutional Ethics Board (protocol number 48370515.4.0000.5273).

Patients presenting with any risk factor predisposing to increased bleeding during or after surgery, such as coagulopathies, chronic kidney disease, continuous treatment with oral anticoagulants, and secondary OA, as well as those whose surgical procedure lasted > 2 hours, were excluded.

The sample size was determined by similar studies in the literature,⁹ and allocation in 2 experimental groups, with 32 patients each, was performed by randomization using sealed envelopes. The envelopes were opened just prior to the closure of the wound, to avoid any kind of bias. Patients in the intervention group (Sealant) received a topical, 6 mL application of Evicel fibrin hemostatic agent, consisting of human fibrinogen (250 to 450 mg) and thrombin (4,000–6,000 IU); these chemicals come in 2 separate vials and they

are combined through an application device. Patients in the control group (Control) received no product application.

All of the selected patients underwent the same standard surgical technique (cemented unilateral primary TKA with posterior stabilization) under pneumatic ischemia; the procedure was performed by surgeons with > 5 years of experience. Three implant models were used: Press Fit Condylar Sigma DePuy-Synthes (Johnson & Johnson, New Brunswick, NJ, USA), NexGen Knee Replacement System (Zimmer Biomet, Warsaw, IN, USA), and ACS Knee System (Implantcast, Hamburg, Germany).

The pneumatic cuff was kept inflated until the wound was completely closed, preventing blood loss throughout the surgical time. A single 4.8-mm intra-articular Hemovac (Zimmer Biomet, Warsaw, IN, USA) drain with negative suction was used in all of the patients and was maintained for 24 hours. Thromboembolic events were prevented in all of the patients through a single daily subcutaneous dose of 40 mg of low molecular weight heparin; this treatment was initiated 12 to 24 hours after the end of the procedure and was maintained for 15 days.

The hematimetric indexes were measured preoperatively, on the 1st postoperative day (24 hours, $n = 63$), and on the 3rd postoperative day (60 to 72 hours, $n = 41$) on those patients who had not yet been discharged.

The following parameters were considered for blood loss analysis: blood volume, blood loss at the drain, hemoglobin loss, and total blood loss.

The blood volume of each patient was determined according to the Nadler formula.¹⁴ The drained blood loss volume was determined by the blood volume (mL) collected by negative suction through the Hemovac drain within 24 hours after the procedure.

Hemoglobin (Hb) loss after 24 hours was calculated using the formula:

Lost Hb = [Hb at admission – Hb at discharge (24h)] + transfused Hb

Where:

1. Lost Hb = total hemoglobin (g/dL) loss after the procedure
2. Hb at admission = Hb (g/dL) \times volemia/100
3. Hb at discharge = Hb (g/dL) \times volemia/100

Transfused Hb = total hemoglobin (g/dL) amount transfused through packed red blood cell transfusion. Each blood bag from the institution and state blood bank contains a mean hemoglobin concentration of 60 g/bag (0.6 g/dL).

The loss of hemoglobin after 60 hours was calculated with the following formula:

Lost Hb = [Hb at admission – Hb at discharge (60h)] + transfused Hb

The blood loss (mL) on the 1st postoperative day (24 hours) was calculated by the following formula:

Blood loss = volemia \times lost Hb (24h)/Hb at admission

The blood loss (mL) on the 3rd postoperative day (60 hours) was calculated by the following formula:

Blood Loss = volemia \times lost Hb (60h)/Hb at admission

Data from all of the patients who received blood transfusions and the number of blood components bags used in each one of them was recorded.

The total length of hospital stay was analyzed and compared between the groups. The discharge criteria were pain control with oral analgesic agents and the ability to walk with assistance, in addition to the absence of clinical complications.

Pain intensity was assessed in all of the patients through a visual analogue scale (VAS), whose score ranges from 1 to 10. The information was collected at the hospital, prior to surgery, and again on the 2nd day and on the 6th week after the procedure.

The ROM was evaluated with the patient in the supine position using a standard goniometer.

Complications, such as wound healing problems, deep venous thrombosis, and superficial or deep infection, were recorded if identified.

All data were analyzed by GraphPad Prism 5 for Windows (GraphPad Software, Los Angeles, CA, USA). The results were presented with the corresponding standard deviation (SD) of the mean. The Fisher exact test was used to compare the gender ratio between the groups. Age, weight, height, body mass index (BMI), blood volume, blood loss drained after 24 hours, loss of hemoglobin after 24 and 60 hours, blood loss after 24 and 60 hours, and length of hospital stay were analyzed by unpaired Student *t* tests. Pain (VAS) and ROM were analyzed by two-way analysis of variance (ANOVA)

Table 1 Gender, age, weight, height, body mass index, and volemia in the control and sealant groups

	Control Group $n = 31$	Sealant Group $n = 32$	<i>p</i> -value
Gender	5 male and 26 female patients	4 male and 28 female patients	0.76
Age (years old)	69.48 \pm 1.27	69.19 \pm 1.21	0.86
Weight (kg)	81.71 \pm 2.0	78.43 \pm 1.69	0.21
Height (m)	1.60 \pm 0.01	1.58 \pm 0.01	0.47
BMI	31.81 \pm 0.73	31.23 \pm 0.72	0.57
Volemia (mL)	4450 \pm 110	4270 \pm 80	0.10

Abbreviation: BMI, body mass index.

Values indicate mean \pm standard deviation of the mean.

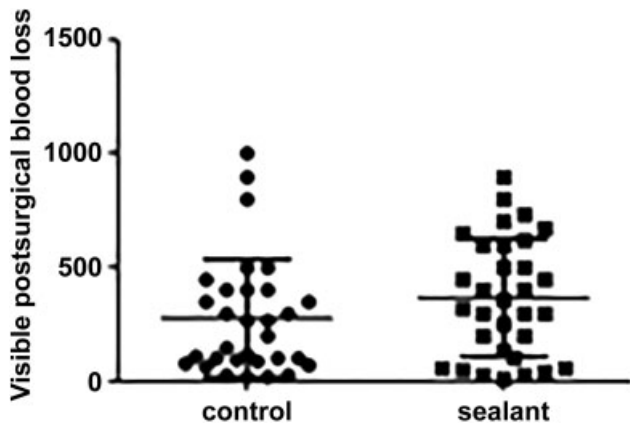


Fig. 1 Blood loss quantified at the drain after 24 hours. Unpaired Student t test.

followed by a post-hoc Bonferroni test after a paired Student t test. A value of $p < 0.05$ was considered statistically significant in all of the analyses.

Results

Of the 64 patients included in study, 1 patient in the control group was excluded from the results evaluation because the surgical procedure lasted > 2 hours until total closure of the wound. Thus, 32 patients received the hemostatic agent and 31 patients did not receive it. The treatment and control groups were similar in terms of basic features, such as gender, age, weight, height, BMI, and blood volume (\rightarrow Table 1).

Regarding the bleeding volume at the drain in 24 hours, there was no significant difference between the groups (Control, $276.5 \text{ mL} \pm 46.24$ versus Sealant, $365.9 \text{ mL} \pm 45.73$; $n = 63$; $p = 0.17$) (\rightarrow Fig. 1).

There was no significant difference between the groups regarding the mean Hb loss in 24 hours (Control, $2.78 \text{ g/dL} \pm 0.24$ versus Sealant, $2.85 \text{ g/dL} \pm 0.24$; $n = 63$; $p = 0.41$) (\rightarrow Fig. 2).

There was no significant difference between the groups regarding the mean Hb loss in 60 hours (Control, $3.69 \text{ g/dL} \pm 0.39$ versus Sealant, $3.85 \text{ g/dL} \pm 0.33$; $n = 41$; $p = 0.37$) (\rightarrow Fig. 3).

There was no significant difference between the groups regarding the mean total blood loss in 24 hours (Control, $930 \text{ mL} \pm 78$ versus Sealant, $890 \text{ mL} \pm 67$; $n = 63$; $p = 0.35$) (\rightarrow Fig. 4).

There was no significant difference between the groups regarding the mean total blood loss in 60 hours (Control, $1,250 \text{ mL} \pm 120$ versus Sealant, $1,190 \text{ mL} \pm 96$; $n = 41$; $p = 0.34$) (\rightarrow Fig. 5).

Only one patient from the control group was transfused with a bag of packed red blood cells. No patient in the Sealant group required transfusions.

There was no significant difference between the groups regarding the length of hospital days stay (Control, 5.61 ± 0.50 ; $n = 31$ versus Sealant, 4.81 ± 0.36 ; $n = 32$; $p = 0.10$) (\rightarrow Fig. 6).

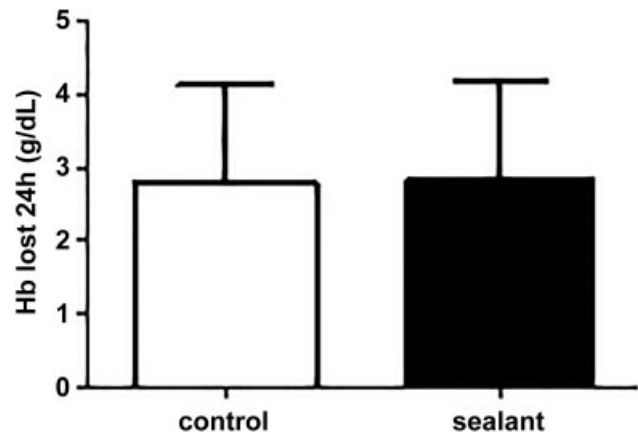


Fig. 2 Mean hemoglobin (Hb) loss 24 hours after surgery, where Lost Hb = [Hb at admission - Hb at discharge (24 h)] + Hb transfused. Unpaired Student t test.

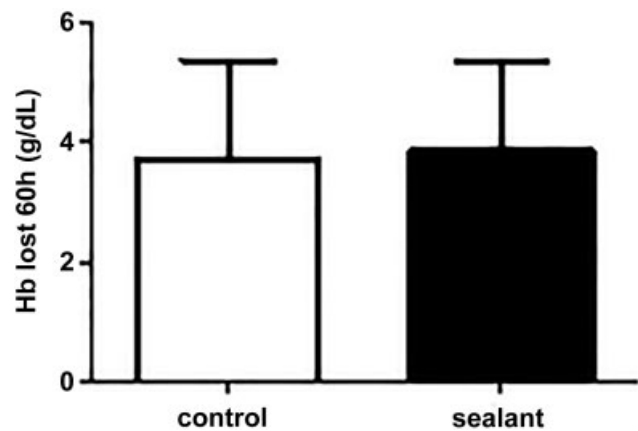


Fig. 3 Mean hemoglobin (Hb) loss 60 hours after surgery, where Lost Hb = [Hb at admission - Hb at discharge (60 h)] + Hb transfused. Unpaired Student t test.

Regarding the VAS, although the pain decreased in both groups over time, there was no significant difference between the Control and Sealant groups ($p > 0.05$) (\rightarrow Table 2 and \rightarrow Fig. 7).

The mean ROM over time is detailed in \rightarrow Table 3. The ROM was higher in the Sealant group compared with the Control group on the 2nd postoperative day ($p = 0.01$), but there was no significant difference in the 6th week ($p = 0.13$) (\rightarrow Fig. 8).

There were no complications, that is, wound healing problems, deep vein thrombosis, or infections, in any of the groups.

Discussion

Regarding the volume of drained blood in 24 hours, we have observed a greater bleeding in the study group compared with the control group, but with no statistical significance. Skovgaard et al,¹⁵ in a prospective, double-blind, placebo-controlled study evaluating 24 patients (48 knees) undergoing simultaneous bilateral TKA, in which 1 knee received a topical, 10-mL application of Evicel fibrin sealant, and the

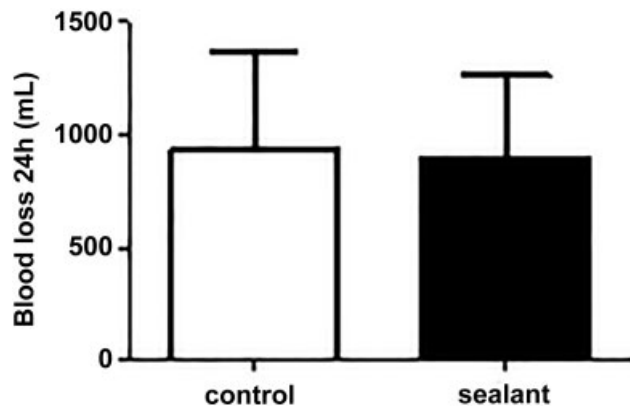


Fig. 4 Mean blood loss 24 hours after surgery, where blood loss = Volemia x lost Hb (24h)/Hb at admission. Unpaired Student t test.

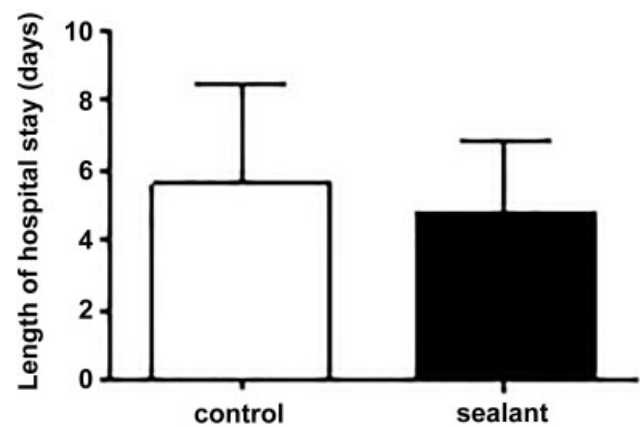


Fig. 6 Length of hospital stay, from surgery to hospital discharge. Unpaired Student t test.

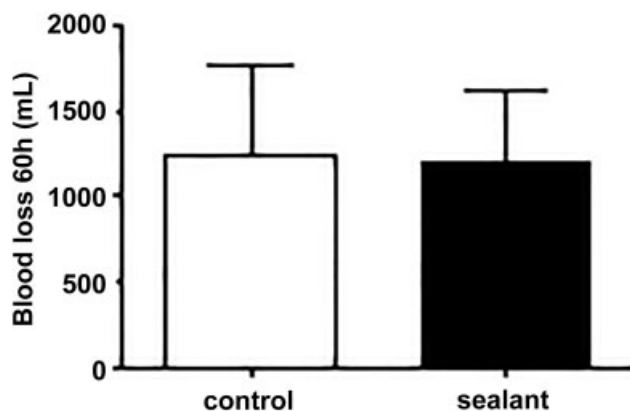


Fig. 5 Mean blood loss 60 hours after surgery, where Blood Loss = Volemia x lost Hb (60 h)/Hb at admission. Unpaired Student t test.

other knee received saline solution, did not observe significant differences regarding the lost blood volume at the drain in 24 hours. Heyse et al¹⁶ evaluated 200 patients in a prospective, double-blind, randomized TKA study in which 100 patients received a topical, 10-mL application of Evicel, and 100 patients received no further intervention. The blood loss in the drain after 24 hours was significantly higher in the study group (780 versus 673 mL; $p = 0.029$). This higher blood loss in the study group could be explained by a “rebound effect” resulting in an increased bleeding after the degradation of this artificial clot by endogenous plasmin.

We did not observe a significant difference between the groups regarding the mean Hb loss 24 and 60 hours after the surgery. Maheshawari et al¹⁷ assessed retrospectively the efficacy of Evicel fibrin sealant (113 patients) compared with a control group (70 patients), and did not observe significant differences in Hb levels on each of the 1st 3 postoperative days.

There was no significant difference regarding the total blood loss between the groups. Similar results were obtained by Randeli et al.⁴ These authors conducted a study to verify if, compared with a control group, topical application of a new fibrin sealant (Evicel) in patients undergoing primary TKA would reduce the perioperative blood loss. A total of 62 patients were randomized to receive the topical Evicel

Table 2 Visual analog scale score over time in both groups

	Control Group	Sealant Group	p-value
VAS, admission	6.16 ± 0.33	6.15 ± 0.43	0.99
VAS, 2 nd day	2.58 ± 0.18	2.75 ± 0.30	0.63
VAS, 6 weeks	0.59 ± 0.14	0.71 ± 0.13	0.52

Abbreviation: VAS, visual analogue scale.

Values indicate mean ± standard deviation of the mean.

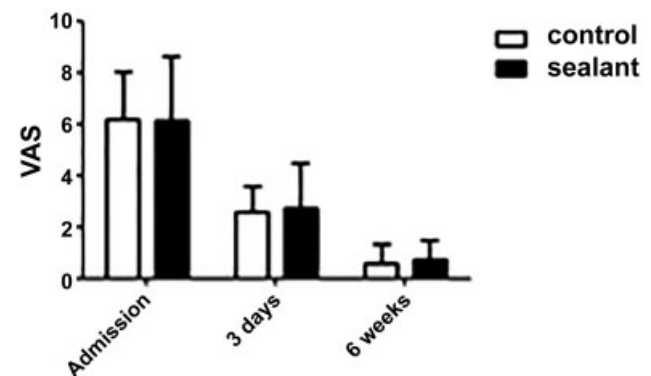


Fig. 7 Mean visual analog scale (VAS) score reported by patients from both groups over time (from to 2 days and 6 weeks postoperatively; analysis by two-way ANOVA followed by a post hoc paired Student t test).

application ($n = 31$) or not ($n = 31$). The perioperative blood loss was similar between the groups (1,900 mL in the control group, and 1,800 mL in the treatment group; $p = 0.4$). Likewise, Heyse et al¹⁶ also found no differences in total blood loss between their groups (1,409 mL in the control group versus 1,441 in the intervention group; $p = 0.44$).

Reinhardt et al¹³ observed that the total blood loss was similar in a retrospective cohort of 114 patients submitted to TKA, in which 1 group received the topical fibrin sealant (Evicel), and another group was submitted to a local infiltration containing epinephrine. Considering that local

Table 3 Range of motion over time

	Control Group	Sealant Group	p-value
ROM, admission	82.4° ± 19.3°	87.8° ± 20.1°	0.28
ROM, 2 nd day	76.7° ± 13°	84.3° ± 9.7°	0.01
ROM, 6 weeks	89.8° ± 8.8°	92.8° ± 6.3°	0.13

Abbreviation: ROM, range of motion.

Values indicate mean ± standard deviation of the mean.

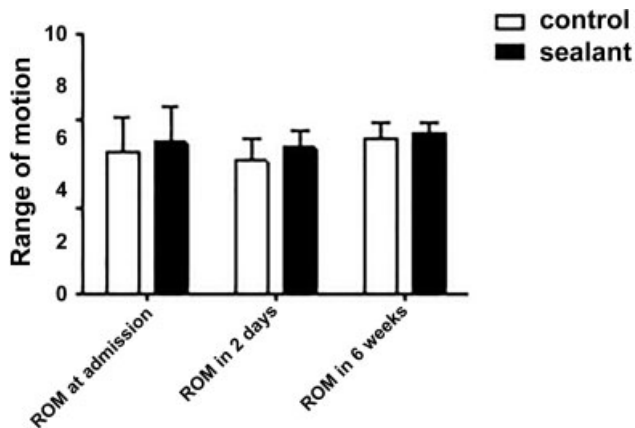


Fig. 8 Mean range of motion (ROM) over time, measured with a goniometer. Analysis by two-way ANOVA followed by a post hoc paired Student t test.

periarticular epinephrine injection reduces bleeding rates after TKA, the use of fibrin sealant may be considered effective. The author points out a possible selection bias resulting from the retrospective nature of the study and the lack of randomization.

In our study, one patient from the control group and none from the study group received blood transfusions. Randelli et al⁴ and Maheshwari et al¹⁷ found similar blood transfusion rates in study and control groups, suggesting that the use of fibrin sealant has no effect on these rates.

Bou Monsef et al³ retrospectively evaluated 176 patients undergoing TKA and compared the effect of a cell saver, a fibrin sealant (Evicel 5 mL), autologous preoperative donation, and no intervention on perioperative bleeding and blood transfusion requirement. All of the strategies resulted in a significant reduction in the need for allogeneic blood transfusion over the control group, suggesting that the use of Evicel was an effective measure compared with the other therapeutic strategies.

Regarding the length of hospital stay, there was no significant difference between the groups. In the study by Randelli et al,⁴ there was also no significant difference between the groups.

Analyzing postoperative ROM and pain according to VAS scores over time, we did not identify any significant difference between our groups, except for ROM on the 2nd postoperative day, which was higher in the study group; this outcome, however, was not sustained until the 6th

week evaluation. We are not able to explain this difference. Reinhardt et al¹³ did not observe a significant difference between ROM after 6 weeks postoperatively. Skovgaard et al¹⁵ also did not observe a significant difference between their groups regarding functional recovery, swelling, pain, knee extension strength and ROM 21 days after the surgery. Heyse et al¹⁶ also did not observe any difference regarding ROM gain and VAS between the intervention and control groups.

No studies in the literature have reported wound healing problems, infections, or thromboembolic complications related to the use of Evicel; similarly, none of these complications were observed in our study.

A highlight of our study is its prospective, randomized, controlled, and unicentric design, as well as the establishment of well-defined inclusion criteria; as such, the treatment and control groups were very similar in terms of basic features, such as gender, age, weight, height, BMI, and blood volume.

A limitation of our study was the loss of patients at the 3rd day evaluation, between 60 and 72 hours postoperatively. We believed that it would not be wise to keep hospitalized patients in discharge conditions just to have these data.

Conclusions

We have concluded that human fibrin hemostatic agent free of clot-stabilizing agents was not effective in reducing the bleeding volume or blood transfusion requirements in TKA patients, and that its use was not able to interfere positively or negatively with the length of hospital stay, pain and ROM. Its use was not related to any complications.

Conflicts of interests

The authors have no conflicts of interests to declare.

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