





## Original Research Article

# Application of a topical collagen agent after tooth extraction to control hemostasis should be immediate and not delayed: a comparative randomized trial

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**Abstract – Objective:** The main objective was to demonstrate that the delay of placement of a collagen-based hemostatic cylindrical dressing, here ETIK COLLAGENE, affects postoperative bleeding. Other objectives were to evaluate the safety of this medical device. **Material and methods:** 38 patients under antithrombotic treatment and consulting for tooth extraction were included. The antithrombotic treatment was maintained. Patients were randomized:

- In group 1: the hemostatic dressing ETIK COLLAGENE was applied immediately after the tooth extraction and curettage; the surgeon assessed the presence of bleeding (Yes/No) every 30 s up to a total time of 8 min, then he sutured.
- In group 2: the bleeding was assessed every 30 s up to a total time of 8 min immediately after the tooth extraction and curettage, then the surgeon placed ETIK COLLAGENE before suturing.

Seven days later, patients were asked about the occurrence of bleedings and adverse events. **Results:** The mean bleeding time after tooth extraction was of 1:13 ± 0:49 (min: sec) and 3:39 ± 3:06 respectively in the group 1 and in the group 2; the difference between groups is 2:26 (95% CI [0:52 – 4:01]) in favor to the group 1 ( $p = 0.0144$ ). There were significantly more adverse effects in group 2. **Conclusions:** The delay in placement of ETIK COLLAGENE after extraction has an impact on bleeding time and postoperative adverse events: these parameters are reduced in a statistically significant way when the placement is performed immediately after the end of the curettage rather than after an 8 min delay.

## Introduction

Tooth extraction is one of the most common invasive oral surgical procedures carried out in routine dental practice [1]. This intervention can be complicated by bleeding during or after surgery and this is more prevalent in patients taking antithrombotic medications [2]. In healthy patients, bleeding can be controlled using conventional methods such as sutures followed by a local compression with a sterile gaze applied firmly for at least 10 min in case of significant hemorrhage. However, the combination of several risk factors (*e.g.*, age and comorbidity, medication and diet, unfavorable local conditions) can lead to a clinical situation with a moderate or high

risk of bleeding [3]. Absorbable hemostatic sponges are used in patients with moderate or high risk of bleeding or in second intention in healthy patients when conventional method cannot allow to control the bleeding.

Post-extraction bleeding is defined as bleeding that continues beyond 8 h after dental extraction. If post-extraction bleeding is not managed, complications can range from soft tissue hematomas to severe blood loss [1].

In case of low-risk oral surgery such as dental avulsions, periodontal surgery or dental implants, the patient treated by antithrombotic drugs (antiplatelet agent, heparin, direct oral anticoagulants (DOAC), vitamin K antagonist (VKA) (with INR <4, measure <24 h or 72 h if INR stable)) continues antithrombotic therapy and a hemostatic agent is used in addition to conventional measures (sutures and compression)

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[3]. If there is a doubt about how to proceed, the prescribing cardiologist must be consulted before suspending the antithrombotic treatment, because patients are more at risk of permanent disability or death if they stop antiplatelet medication prior to a dental procedure than if they continue it [2]. In the case where the patient's physiological coagulation is impaired (Von Willebrand's disease, Hemophilia A or B), the European Medicines Evaluation Agency (EMA) recommends the use of products derived from human blood (fibrinogen, thrombin) in addition to conventional techniques [4].

The hemostatic agents used intra-alveolar are oxidized cellulose, resorbable gelatin sponges, collagen sponges, fibrin glue, cyanoacrylate glue, plasma gel rich in platelets, calcium alginate, chitosan [1,5]. An antifibrinolytic, tranexamic acid, used in mouthwashes or on a compress is also used [6].

The collagen sponges are part of topical hemostatic agents used in oral surgery. Collagen is a tissue protein found in the media of blood vessel walls. When vascular breaches appear, circulating platelets are exposed to collagen, adhere to these fibers, and initiate their activation process: the platelets release clotting factors, activate the endogenous pathway and platelet aggregation takes place. The supply of exogenous collagen, like collagen cylinder, molds itself into the hemorrhagic surface where it adheres strongly upon mechanical compression, thus promoting the formation and maintenance of a platelet clot and participates in the activation of coagulation [7,8].

ETIK COLLAGENE is a collagen hemostatic dressing manufactured by Products Dentaries Pierre Rolland since 1991 and CE-marked since March 2000. As well as other hemostatic sponges, this product consists of collagen derived from purified and lyophilized bovine flexor tendon (native, non-denatured with 80–90% type I collagen and 10–20% type III collagen). It is available as a sterile, single-used and absorbable cylinder. ETIK COLLAGENE can be used in adults or children. ETIK COLLAGENE is recommended in patients on antithrombotic medication (such as antiplatelet agent, DOAC, VKA treatment) in addition to conventional sutures and local compression. It is intended for use in tooth socket following tooth extraction, or in a small operating field.

Currently, the few studies conducted have studied patients on VKA and the heterogeneity of the methodologies reported in the included studies did not allow the performance of meta-analyses, moreover the included studies were all at moderate/high risk of bias [9]. A recent systematic review concluded that no superiority could be determined for one hemostatic agent over the others on patients treated with Warfarin (VKA) [10]. Another recent systematic review concluded that there is a lack of clinical studies on the efficacy of intra-alveolar devices on post-dental extraction bleeding in patients on DOAC and anti-platelet agents [9]. It is legitimate to ask whether the use of a collagen hemostatic agent is effective on bleeding in patients taking antithrombotic, and, to ask whether the way in which this agent is used has an impact on its effectiveness.

The main objective is to demonstrate that the delay of placement of a collagen-based hemostatic surgical dressing affects immediately postoperative bleeding in patients with risk for bleeding, such as patients undergoing oral anticoagulant therapy, antiplatelet therapy, or anti-vitamin K therapy. Tooth extractions take place without interruption or modification of the antithrombotic treatment as recommended by the French Society of Oral Surgery in 2015 [3].

The secondary objectives are to assess secondary bleeding up to seven days after surgery, the patient's pain, or discomfort during and after the procedure, safety of (ETIK COLLAGENE).

## Material and methods

### Study design

The study was a prospective, randomized, controlled and comparative clinical investigation. The study was carried out in the Rennes University Hospital and Nantes University Hospital. It received the approval of the Ethic Committee on 12/16/2021 and is registered under the French National Agency number 2021-A02568-33 and the NCT05174858.

The present study was simple-blinded, meaning that the investigator knew which treatment group was allocated to the patient, but the patient was blinded to the treatment.

Recruitment took place over 4 months, from January to May 2022, and each patient was followed for 7 days after the intervention.

Participants were patients with antithrombotic drugs or moderate thrombocytopenia who had a dental avulsion. One tooth per patient was included in the protocol. Patients were randomized into two groups formed with a 1:1 ratio.

Patients randomized in Group 1 received the placement of ETIK COLLAGENE (1 or 2 cylinders) in the tooth socket immediately after tooth extraction. Patients in Group 2 were in the control group; ETIK COLLAGENE cylinders were not immediately placed after tooth extraction, it was delayed of 8 min. Based on recent publications, the maximum hemostasis time values range from 3 min to 7 min 20 s (5,11–16). Thus, to avoid bias, the bleeding time was evaluated over a period of 8 min in this clinical study before suturing the surgical site.

The data were collected by an electronic case report form and a paper document was given to the patient, with an auto-questionnaire for the 7-days follow-up.

### Outcome measures

The primary endpoint was the assessment of immediate bleeding (bleeding time) in two groups in which the hemostatic topical was not applied at the same time. Bleeding time was measured by assessing the presence of bleeding within the first 8 min post-extraction.

The secondary outcome measures were bleeding after 20 min, occurrence of secondary post-extraction bleeding at 7 days after surgery and the pain with the use of a numeric scale (0 no pain and 10 the worst) at the end of the surgery, up to day 7. The safety was evaluated by the occurrence of adverse events like allergy, local oedema, alveolitis.

## Eligibility criteria

The inclusion criteria were adults (>18 years old) coming for the extraction of one or more teeth and taking antithrombotic treatment (antiplatelet agent, heparin, DOAC, VKA with  $1.5 \leq \text{INR} \leq 3$  during the last 24 h), or with a moderate thrombocytopenia (80 000–150 000 platelets/mm<sup>3</sup>). The patient signed a written informed consent form and agreed to be contacted by telephone the days after the surgery.

If a patient was requiring multiple dental avulsions in the same session, only one tooth was included in the study and the patient could only be included once in the study. There was no modification or interruption of the antithrombotic treatment for the surgery [3].

The main exclusion criteria were: known allergy to bovine collagen, preoperative INR < 1.5 or > 3 or instable (only for patient treated with VKA), patient with high risk of bleeding (ex: hemophilia, severe thrombocytopenia (<80 000 platelet/mm<sup>3</sup>), history of postoperative hemorrhagic complication, alcoholism...), treatment with bone resorption inhibitor or patient irradiated at the cervico-facial level, contraindication to anaesthesia using articaine with 1:200,000 epinephrine, and presence of uncontrolled hypertension, uncompensated diabetes.

## Intervention

During the first consultation, consent was obtained and explanations about the surgery were given. The dental extraction was performed in accordance with the standard of care and under local anaesthesia. It was performed with carpules of Epinephrine 1:200,000 to standardize the vasoconstrictor effect which impacts on hemostasis.

Immediately after tooth extraction and curettage of the granulation tissue, the bleeding assessment (T0) was recorded and the ETIK COLLAGENE cylinders' timing placement was done according to the randomization group:

- Group 1: immediate placement of cylinders of ETIK COLLAGEN in the alveolus.
- Group 2: alveolus empty during 8 min after curettage; the placement of ETIK COLLAGEN is delayed.

Regardless of the group, a sterile and dry gauze was placed on the surgical site to protect the wound. The dental assistant started the stopwatch for the measurement of bleeding time:

- Every 30 s up to a total time of 8 min: the surgeon lifted the gauze and observed the tooth socket for 5 s, recorded the presence of bleeding (Yes/No), and then replaced the protection gauze.
- At the end of the 8 min bleeding evaluation time:
  - Group 1: the surgeon sutured.
  - Group 2: the surgeon placed cylinders of ETIK COLLAGENE in the alveolus and sutured.

In the group 1, the stopwatch was started right after the insertion of the cylinders in the alveolus, and in the group 2, the stopwatch was started directly at the end of the curettage.

If the cylinder insertion delay is not considered for the group 1, the bleeding time is artificially reduced. Therefore, 20 s per cylinder were added to the measured bleeding time (corresponding to the time estimated for the insertion of cylinder into the tooth socket).

Patients were kept under surveillance for 10 min with local compression and it was recorded if a bleeding was still present (*i.e.*, around 20 min after the end of the intervention). In case of bleeding, the patient continued the local compression with a gauze soaked in tranexamic acid.

For patients with several avulsions planned in the same session, the extractions were carried out in 2 stages: the tooth included in the protocol was extracted and studied separately from the other teeth which were not included in the study; thus, the entire protocol was carried out on the included tooth (avulsion, bleeding time assessment (placement of ETIK COLLAGEN), suture) without the extraction of the other teeth causing any bias.

## Sample size

Based on recent and peer-reviewed articles [5,11–16], the mean time to hemostasis is 1:23 min:sec (SD=0:47) after tooth extraction with a topical hemostatic agent and 2:47 min:sec (SD=1:11) with placebo or sterile gauze (control group). The global SD is 0:59 min:sec.

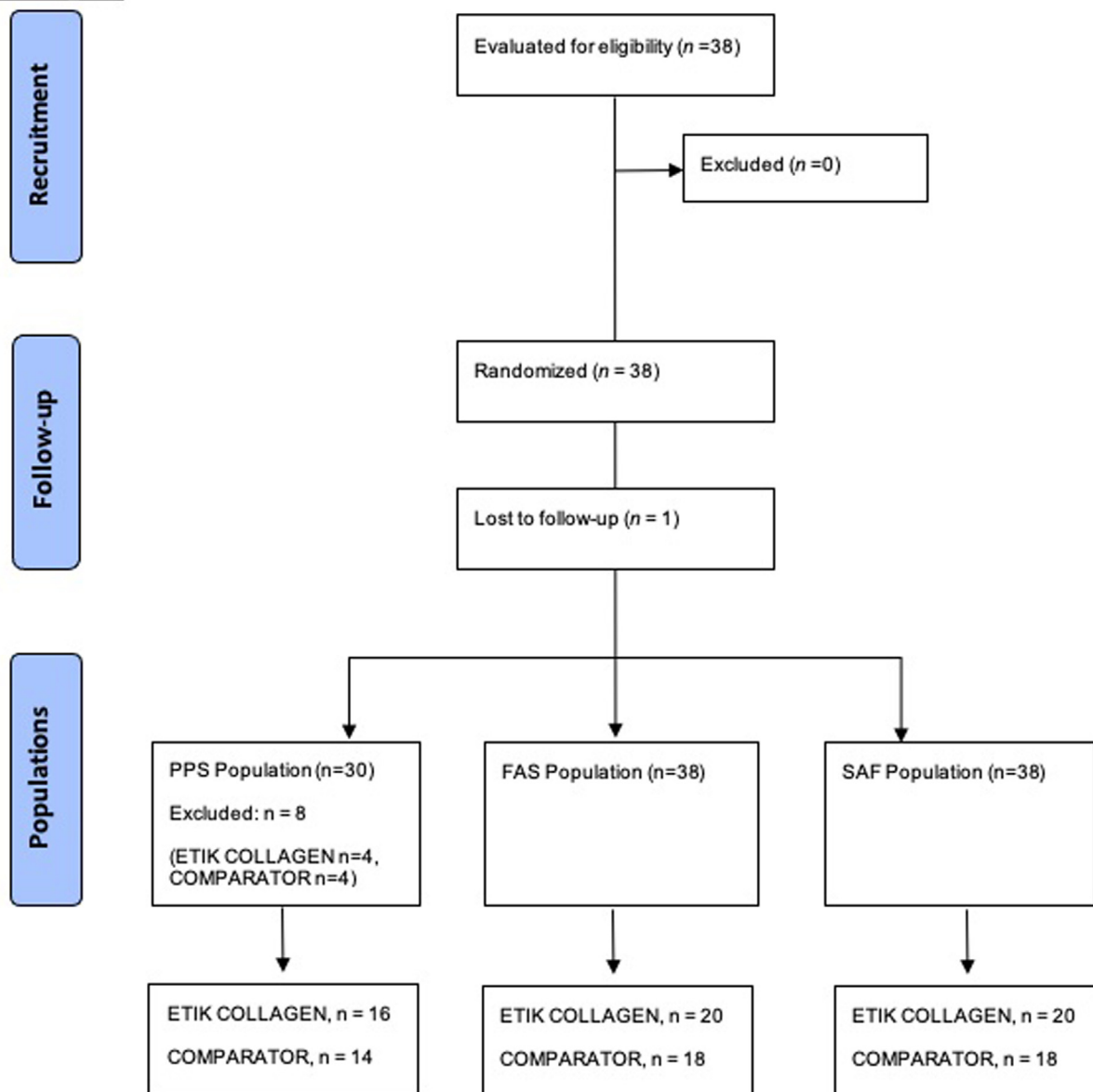
For a superiority trial with a type I error probability set at 5% (two-sided), a power of 80%, a SD of 1 min, 10% of drop-out and a difference in means of 1 min, the number of subjects to include is 19 per group, *i.e.*, a total of 38 patients.

## Statistical analysis

Statistical analyses were run using JMP<sup>®</sup> from SAS institute version 15.0.0. All the analyses were two-tailed tests with an alpha level of 5%. Patients were analyzed according to the intention to treat principle; all patients randomly assigned to a treatment group were analyzed, namely according to the treatment they were randomized to receive: it is the Full Analysis Set (FAS). Additional analyses were also run to support the results, which only included participants without any major deviations from the protocol (defined as a deviation with a significant impact on the primary endpoint, such as a missing or non-interpretable data): it is Per Protocol analysis Set (PPS). For safety analyses, patients were analyzed according to the treatment they really received: it is the Safety Analysis Set (SAF).

Descriptive statistics were presented according to the type of data: means and medians for the quantitative variables along with measures of dispersion (standard deviation and range), and frequencies/percentages for the nominal variables. The values obtained were compared between the two groups using Wilcoxon non-parametric tests for the quantitative variables, and Chi-squared tests or Fisher's exact tests for the nominal variables.

**Flow diagram**



**Fig. 1.** Flow chart of population.

**Results**

**Population**

– Flow chart (Fig. 1):

38 patients were informed and signed an informed consent form. 19 were recruited by each center.

3 patients interrupted their antithrombotic treatment for the intervention, this is considered as a major deviation. 6

major deviations (of which one patient also interrupted his antithrombotic treatment) were caused by a delay of the investigator at the end of the tooth extraction leading to a failure to follow the protocol planned timeline.

All patients with at least one major deviation were excluded from the PPS (*i.e.*, 8 patients).

There was one lost to follow-up because a patient in group 2 came to the surgery but did not answer the phone after the 7th day. The primary endpoint was collected.

**Table I.** Population characteristics.

Population		Group 1 n = 20	Group 2 n = 18	Total n = 38
Age (in years)	Mean	67.4	74.5	70.8
	SD	14.2	11.0	13.1
	Median	72.4	76.3	73.7
	Minimum	33.8	52.7	33.8
	Maximum	87.3	91.6	91.6
Gender (n)	Males	15 (75.0%)	11 (61.1%)	26 (68.4%)
	Females	5 (25.0%)	7 (38.9%)	12 (31.6%)
Smoking status (n)	Smoker	3 (15.0%)	2 (11.1%)	5 (13.2%)
	No or former smoker	17(85.0%)	16 (88.9%)	33 (86.8%)
Reason for the hemostasis disorder (n)	Thrombotic drugs	20 (100%)	18 (100%)	38 (100%)
	Moderate thrombocytopenia	0	0	0
Type of drug (n)	Antiplatelet	11 (55.0%)	10 (55.6%)	21 (55.3%)
	Heparin	0	0	0
	Direct oral anticoagulants	8 (40.0%)	6 (33.3%)	14 (36.8%)
	Anti-vitamin K	1 (5.0%)	2 (11.1%)	3 (7.9%)

*n* = number of patients; SD = Standard Deviation.

#### – Description of the FAS population

Included and randomized patients were aged in mean of  $70.8 \pm 13.1$  years (range: 33.8 to 91.6 years). The population's sex ratio was in favor of male (68%) and was composed of more no smokers (1 smoker for 6 no smokers).

The cause of change in hemostasis was taking antithrombotic treatment for all patients. No patients were recruited for platelet deficiency. The prescription of antithrombotic was at 55.3% of antiplatelet, 36.8% of DOAC and at 7.9% of VKA (Tab.I). Proportions were similar in both randomization groups.

At inclusion, all patients had one or several balanced pathology (ies), mainly cardiovascular pathologies (51.0%) and metabolic disorders (16.1%). Pathologies description was similar in both randomization groups.

Among 38 included patients, 39.5% of patients required the removal of a single tooth, 28.9% required the removal of 2 teeth, 23.7% required the removal of 3 teeth and 7.9% of patients had more than 3 teeth to avulse. The assessment of patient safety by maintaining low bleeding risk was reviewed with each new tooth extracted during the surgery.

A total of 38 teeth were analyzed for this study, 20 in group 1 and 18 in group 2. Table II presents the characteristics of the teeth; description is similar in both randomization groups with a proportion of molar (47.4%) higher than for other types of teeth.

Concerning the anaesthesia: Epinephrine 1:100,000 was used for one patient in the group 1 and one in the group 2. Epinephrine 1:100,000 is twice more concentrated than

Epinephrine so the 1:100,000 epinephrine carpules were replaced by twice the number of 1:200,000 epinephrine carpules. Considering the site of the study tooth, most patients ( $n = 25$ ; 65.8%) only needed one carpule (Tab. III).

About the number of cylinders used: in the group 1, 75% of the patients needed one cylinder and 25% needed two cylinders according to the tooth socket size. In the group 2, 72.2% of the patients needed 1 cylinder and 27.8% needed 2 cylinders.

#### Primary outcome: bleeding time (Fig. 2)

The tooth extraction ended with the step of the alveolus curettage, 6 patients were not bleeding right after the curettage (T0), 3 in the group 1 and 3 in the group 2 in the FAS population.

The mean bleeding time was of  $1:13 \pm 0:49$  (min:sec) and  $3:39 \pm 3:06$  (min:sec) respectively in the group 1 and in the group 2 in the FAS population. The difference between both groups in the duration of bleeding was 2:26 (95% CI [0:52–4:01]) (min:sec) in favour of immediately use of ETIK COLLAGEN compared to the empty tooth socket. The bleeding time after a tooth extraction is significantly lower for patients receiving ETIK COLLAGENE cylinders immediately after the end of the curettage, compared to patients receiving ETIK COLLAGENE cylinders 8 min after the end of the curettage ( $p = 0.0144$ ).

No persistent bleeding occurred over 3:15 (min:sec) in the group 1. In the group 2, the maximum bleeding time was 8:10 (min:sec) for 4 patients, which corresponds to the maximum evaluation time.



**Table II.** Description of included teeth.

Population		Group 1 n = 20	Group 2 n = 18	Total n = 38
Tooth arch of included tooth (n)	Maxilla	11 (55.0%)	9 (50.0%)	20 (52.6%)
	Mandibular	9 (45.0%)	9 (50.0%)	18 (47.4%)
Tooth type of included tooth (n)	Incisor	3 (15.0%)	3 (16.7%)	6 (15.8%)
	Canine	2 (10.0%)	2 (11.1%)	4 (10.5%)
	Premolar	5 (25.0%)	5 (27.8%)	10 (26.3%)
	Molar	10 (50.0%)	8 (44.4%)	18 (47.4%)

*n* = number of patients.

**Table III.** Description of anaesthesia at the study tooth site.

Population		GROUP 1 n = 20	GROUP 2 n = 18	Total n = 38
Name of the anaesthetic used	N	20	18	38
	md	0	0	0
	SEPTANEST	20 (100%)	18 (100%)	38 (100%)
Use of « Epinephrine 1 : 200 000 » (n)	Yes	19 (95.0%)	17 (94.4%)	36 (94.7%)
	No	1 (5.0%)	1 (5.6%)	2* (5.3%)
Number of carpules administered at the study tooth site (n)	1	13 (65.0%)	12 (66.7%)	25 (65.8%)
	2	6 (30.0%)	6 (33.3%)	12 (31.6%)
	3	1 (5.0%)	0	1 (2.6%)

\* 2 patients used "Epinephrine 1:100 000" In the following tables, their number of carpules has been multiplied by 2 to be equivalent to "Epinephrine 1:200 000".

*n* = number of patients.

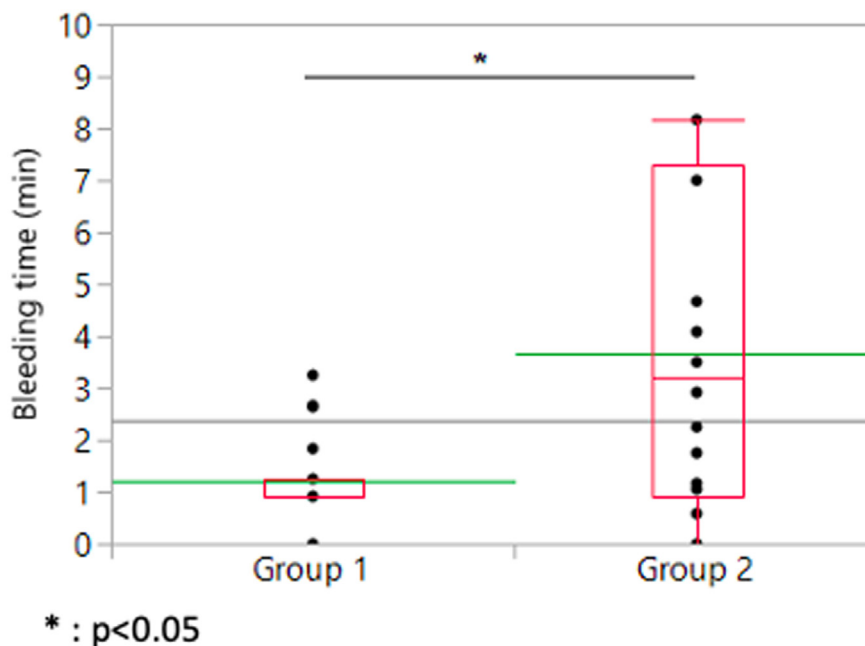
The result of the PPS confirms the result obtained in FAS and the significance of the primary endpoint increase in the PPS compared to the FAS. Indeed, the mean duration of bleeding was  $1:16 \pm 0:54$  (min:sec) and  $4:30 \pm 3:00$  (min:sec) respectively in the group 1 and in the group 2. The bleeding time after a tooth extraction was significantly lower in group 1 ( $p=0.0020$ ). The duration of bleeding was reduced of  $3:14$  (95% CI [1:27–5:00]) (min:sec) in the group 1 compared to the group 2.

### Secondary outcomes

- Bleeding after 20 min and occurrence of secondary post-extraction bleeding for 7 days assessment

In mean, the duration of the procedure was  $24:12 \pm 13:24$  (min:sec) with no significant difference between the randomization groups ( $p=0.7251$ ). None of the patients was still bleeding 20 min after the tooth extraction.

A total of 13 patients (out of 37) (35.1%) noticed at least one secondary post-extraction bleeding during the 7 days following the dental avulsion; 7 (35.0%) in the group 1 and 6 (35.3%) in the group 2 ( $p=0.9851$ ). When a secondary bleeding occurred, it was stopped after 10 min compression at 76.7%. Moreover, 2 times for the same patient (randomized in group 1), the bleeding was still ongoing after a second compression period of 10 min and stopped spontaneously during the consultation in the emergency room. The time to onset of secondary bleeding since the suture, was  $8.6 \pm 8.3$  h in the group 1 and  $3.8 \pm 3.0$  h in the group 2 ( $p=0.2221$ ).



**Fig. 2.** Boxplot of bleeding time (minutes: seconds).

– Pain and discomfort after surgery

At the end of the surgical procedure, 97.4% of the patients noticed a complete absence of pain. One patient (group 1) noticed pain at 3 on a numerical scale of [0 to 10]. The anaesthesia was still effective at this time.

64.9% of the patients noticed at least one pain during the 7 days following the tooth extraction, and the mean of maximum pain felt was the same in both groups (on a numerical scale [0–10];  $3.9 \pm 2.3$  vs  $3.9 \pm 2.8$ ). The maximum mean pain is  $3.8 \pm 2.0$  at T6 h and gradually decreased until Day 3 with mean pain  $1.7 \pm 1.0$ . The level of pain was moderate and low according to the HAS' categorization (0: no pain, 1–3: low pain, 4–5: moderate pain, 6–7 severe pain, 8–10 unbearable pain). At each time, the pain felt was not significantly different between both groups.

– Occurrence of adverse events, complications (...), and device deficiencies (SAF population)

At least one adverse event has occurred for 9 patients (23.7%) corresponding to a total of 10 events. The number of patients with at least one adverse event was significantly different according to the randomization group with 1 patient in the group 1 (for 1 adverse event) and 8 patients in the group 2 (for 9 adverse events) ( $p = 0.0067$ ). 8 of the 9 adverse events noticed in the group 2 were complications (Tab. IV), and one was a serious adverse event not related to the medical device or procedure (hospitalization following a fall with cracked hip). In correlation with the number of patients presenting at least one adverse event, the difference between the number of complications per group is significant ( $p = 0.0140$ ) (Tab. IV).

The severity of adverse event was mild (80.0%) or moderate (20%); the medical device studied can be considered as safe for use. There was no device deficiency.

3 patients (8.1%) consulted a dentist once on an unscheduled visit, for a problem in the operated zone. In group 1 (1 patient) for bleeding and in group 2 (2 patients) for dry socket and inflammation at the suture.

## Discussion

### Population

Hemostasis depends on the dynamic balance between fibrin formation and fibrin resolution. It is a complex interaction between platelets, plasma proteins, coagulation, and fibrinolytic pathways. The coagulation process consists of three main phases: initiation, amplification, and propagation. The initiation phase begins with damage to the endothelium and release of tissue factor (ultimately leading to the formation of thrombin). Platelet aggregation and activation occur during the amplification phase and provide the initial hemostatic response. Finally, fibrin formation and platelet clot stabilization occur during the propagation phase [1]. VKA prevents the activation of clotting factors vitamin K dependents, DOAC are direct thrombin or factor Xa inhibitors [17]. Antiplatelets irreversibly inhibit platelet aggregation and this lasts for the life of the platelets (7–10 days) [16]. Contrary to the majority of studies where the anti-thrombotics studied are VKA [9], the most represented anti-thrombotics in this study are antiplatelet agents (55.3%) and DOAC (36.8%).

At baseline, the 2 groups were comparable in terms of demographic and dental characteristics. Patients on antithrombotics were recruited regardless of their type of antithrombotic treatment to reflect the real life at the hospital. Randomization resulted in two comparable groups despite the different types of anti-thrombotic. In this real-life approach and concerning the INR, the upper limit was 3 and not 4, as

**Table IV.** Description and comparison of complications during the 7 days following treatment in SAF population.

SAF population		Group 1 n = 20	Group 2 n = 18	Total n = 38
Patient with post operative complication during the 7 days following treatment	N	20	17	37
	md	0	1	1
	Yes (n)	1 (5.0%)	7 (41.2%)	8 (21.6%)
	No (n)	19 (95.0%)	10 (58.8%)	29 (78.4%)
	Comparison <i>Fisher exact test</i>	p = 0.0140		
Details of complication	Hematoma on the face (n)	0	1 (14.3%)	1 (11.1%)
	Oedema at the surgical site (n)	1 (100%)	5 (71.4%)	6 (66.7%)
	Infection at the surgical site (n)	0	0	0
	Allergic reaction (n)	0	0	0
	Other adverse reaction related to the surgery (n)	0	2* (28.6%)	2 (22.2%)

(\*) One dry socket and one inflammation around the surgical site.  
n = number of patients; md = missing data; p = p-value; \* =  $p < 0.05$ .

recommended by the French society of oral surgery, because one of the two recruiting centers uses hemostatic glue in addition to hemostatic sponge for patients with an INR between 3 and 4.

### Primary outcome

The mean bleeding time was  $1:13 \pm 0:49$  (min:sec) and  $3:39 \pm 3:06$  (min:sec) respectively in the group where ETIK COLLAGENE was applied immediately after tooth extraction and in the group where ETIK COLLAGENE application was delayed 8 min after tooth extraction. The difference is significant ( $p = 0.0144$ ). The per protocol analysis confirms the results obtained in the FAS. This result can be explained by the properties of collagen which causes platelet aggregation and therefore platelet plug formation at the time of the initial hemostatic response which occurs within the first 5 min of hemostasis [7].

The placement of collagen cylinders immediately after the end of the curettage could be more efficient than the use of others topical hemostatic agents like Chitosan (1:34 min:sec), Platelet-Rich-Fibrin (2:38 min:sec) or Haemocoagulase (1:35 min:sec) [5,12,16]. We can emphasize the effectiveness of these collagen sponges in hemostasis in patients taking antiplatelet agents, DOAC or VKA.

### Secondary outcomes

In this trial, 97.4% of the patients notified a complete absence of pain at the end of the intervention; it should be noted that the anaesthesia was always effective. 64.9% of the patients noticed at least one low/moderate pain during the week following the tooth extraction, and the mean of maximum pain felt was not significantly different with  $3.9 \pm 2.3$  in group 1 vs  $3.9 \pm 2.8$  in group 2 (using a numeric scale 0–10). These values can be compared to studies using other intra-alveolar devices: Halfpenny and al. compared the level of postoperative pain in patients who received bovine fibrin or oxidized regenerated cellulose and reported respectively 40% pain (moderate or severe) versus 70% [18]. Their results show more postoperative pain than in this study using collagen sponges. Pippi and al. showed that the patients of the group with the use of a device derived from Chitosan after dental avulsions (a natural biocompatible polysaccharide extracted from the shell of crustaceans) declare a maximum pain of  $3.05 \pm 2.14$  a few hours after the intervention against  $4.30 \pm 2.43$  for patients who received a collagen sponge, without significant difference ( $p = 0.055$ ) [19]. In comparison with our study using collagen sponges, the level of pain is similar.



Few patients (8.1%) had to consult again within 7 days following the intervention, which is consistent with the retrospective study conducted by Svensson in which 6% of patients had to consult again after extraction under VKA and with the use of a collagen or gelatin sponge [20].

The number of patients with at least one adverse event was significantly different with 1 patient in the group where the cylinder of ETIK COLLAGEN was immediately placed after the extraction and 8 patients in the group where the cylinder was placed 8 min after the extraction. It is interesting to note that when several teeth extractions are performed in oral surgery, it seems better to place the collagen sponge in each socket immediately after the extraction of the tooth, and not after having removed all the teeth, to reduce the adverse events. It could be useful to improve the post-operational effect, however additional studies are required.

A new type of collagen, from tilapia fish, has recently been studied for its hemostatic power on artery bleeding in rabbits and rats. The adhesion ability of fish collagen sponge to red blood cells/hemoglobin, and blood coagulation ability are not significantly different from that of bovine collagen sponge [8]. Further studies would be interesting to confirm the results and complete the arsenal of collagenous sponges.

## Conclusion

The present study provides evidence that the placement of the collagen-based hemostatic surgical dressing ETIK COLLAGENE in the socket has an impact on bleeding time: placement of the hemostatic agent in the alveolus immediately after the end of the curettage significantly reduce ( $p = 0.0144$ ) the bleeding time after a tooth extraction in comparison with an empty alveolus.

Considering that patient who received the hemostatic agent immediately after the end of the curettage presents significantly less adverse events than patients who received the cylinder 8 min after the end of the curettage, the delay of insertion of the cylinder seems to have an impact on the occurrence of post-operative complications. The data must be analyzed carefully because of the small sample size of the patients presenting adverse events.

## Conflict of interest

Dr. Flora Thibaut, SLB Pharma, as well as the hospitals (Rennes and Nantes), received compensation from Products Dentaries Pierre Rolland SAS for their active participation in setting up or carrying out the study. The first author and other co-authors did not receive any emulor for the study. The collagen-based hemostatic surgical dressings ETIK COLLAGENE were loaned free of charge by Products Dentaries Pierre Rolland SAS.

## Funding

The sponsor, PRODUITS DENTAIRE PIERRE ROLLAND, provides funding for the clinical investigation. PRODUITS DENTAIRE PIERRE ROLLAND will sign a Civil Responsibility Promoter contract for research with the insurance company HDI-Global SE in France before the regulatory submission, in 2016.

## Ethical approval

The sponsor, investigators and the CRO are committed to conduct this clinical investigation in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and according to medical device regulations (EU Regulation 2017/745 on medical devices, EN ISO Standard 14155:2020 for the clinical investigation of medical devices for human subjects - Good clinical practices). The CIP is written in accordance with Appendix A of EN ISO 14155:2020.

## Informed consent

The patient signed a written informed consent form and agreed to be contacted by telephone the days after the surgery.

## Authors Contributions

The writer was **Anaïs Protin**, resident in oral surgery.

The coordinating investigator was **Dr. Flora Thibaut** (department of oral surgery, Rennes University Hospital). **Dr. Julien Hamon** was a co-investigator in Rennes University Hospital.

There was the participation of the Nantes University Hospital with **Dr. Maxime Guillemain and Pr. Anne-Gaëlle Chau** (department of oral surgery).

**Charlotte Cameli and Anne-Laure Sérandour** belong to the clinical research organization (SLB pharma).

FT: conceptualization, methodology, supervision, writing, review and editing.

CC: conceptualization, methodology, writing, reviewing, and editing.

ALS: conceptualization, methodology, writing, reviewing and editing.

MG: Investigation.

AGC: Investigation.

JH: Investigation.

AP: Writing original draft.

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