A comparison of the mechanical, kinetic, and biochemical properties of fibrin clots formed with two different fibrin sealants

W. Hickerson, MD, I. Nur, R. Meidler

*Blood Coagulation and Fibrinolysis*

This reprint describes pre-clinical data, the clinical significance of which has not been established. This information is being provided in response to a request for medical information and should not be used to make comparative safety or efficacy conclusions.

EVICEL® Fibrin Sealant (Human) is approved as an adjunct to hemostasis for use in patients undergoing surgery, when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.

Omrix Biopharmaceuticals provided funding for this pre-clinical investigation. This article is being disseminated at the expense of ETHICON, Inc.

W.L.H. is on a speaker’s bureau for Johnson & Johnson but has received no compensation for that work. I.N. and R.M. are employees of OMRIX Biopharmaceuticals.

**Full Prescribing Information**

Please see attached full prescribing information for EVICEL® Fibrin Sealant (Human).

**Important Safety Information**

- For topical use only. Do not inject directly into the circulatory system.
- Not indicated for the treatment of severe or brisk arterial bleeding.
- Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products.
- Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants. These events appear to be related to the use of the spray device at higher than recommended pressures and in close proximity to the surface of the tissue. Follow labeled application instructions regarding pressure range and distance when using a spray device and monitor patients for the possibility of air or gas embolism.
- Because this product is made from human plasma it may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeld-Jakob disease (CJD) agent.
- Anaphylactic reactions may occur.
- Most common adverse events reported in clinical trials (≥5%) are bradycardia, nausea, hypokalemia, insomnia, hypotension, pyrexia, graft infection, vascular graft occlusion, oedema peripheral, constipation.
A comparison of the mechanical, kinetic, and biochemical properties of fibrin clots formed with two different fibrin sealants
William L. Hickerson, Israel Nur and Roberto Meidler

The objective of the present study was to compare the mechanical, kinetic, and biochemical properties of fibrin clots produced using EVICEL Fibrin Sealant (Human) and TISSEEL Fibrin Sealant. The stiffness/elasticity and strength of fibrin clots formed with EVICEL and TISSEEL were assessed using applied mechanical force and thromboelastography (TEG). The factor XIII content of the fibrin clots was also evaluated. Mean Young modulus and tensile strength of the fibrin clots produced by EVICEL were significantly higher than those of clots produced by TISSEEL (P < 0.05 for both). The mean time to initial clot formation and mean time to the predefined level of clot formation were numerically shorter for EVICEL compared with TISSEEL. Furthermore, mean maximal amplitude of the clots formed with EVICEL was significantly greater than that for the clots formed with TISSEEL. Mean concentration of factor XIII for the EVICEL fibrinogen samples tested was 9 IU/ml compared with undetectable concentrations of factor XIII for the TISSEEL fibrinogen samples. Fibrin clots formed with EVICEL have a much higher resistance to stretching and tensile strength and are more capable of maintaining their structure against applied force than those formed with TISSEEL. EVICEL also allows more rapid development of fibrin clots than TISSEEL. This superior clot strength and resilience obtained with EVICEL relative to TISSEEL may be due in large part to the presence of factor XIII. Blood Coagul Fibrinolysis 22:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction
A number of fibrin sealants are commercially available, typically consisting of human plasma-derived thrombin and fibrinogen, which are combined and applied to a target bleeding site to achieve hemostasis [1]. Efficacy of these agents has been demonstrated in a variety of surgical settings, including cardiac, thoracic, plastic and reconstructive, gastrointestinal, orthopedic, and neurologic surgery [2–9].

EVICEL Fibrin Sealant (Human) (Johnson & Johnson Wound Management, a division of ETHICON, INC., Somerville, New Jersey, USA), which contains only human components and no aprotinin or tranexamic acid, is indicated as an adjunct for hemostasis in patients undergoing surgery, when control of bleeding by standard surgical techniques is ineffective or impractical [10]. EVICEL is a modification of CROSSEAL Fibrin Sealant (Human) (Johnson & Johnson Wound Management, a division of ETHICON, INC.), in which the plasminogen component has been removed by affinity chromatography using tranexamic acid ligand, alleviating the need for an antifibrinolytic agent, such as aprotinin or tranexamic acid [11].

In contrast, TISSEEL Fibrin Sealant (Baxter Healthcare Corporation, Westlake Village, California, USA) contains plasminogen and synthetic aprotinin [12]. The inclusion of aprotinin is intended to prevent plasmin and plasminogen-mediated fibrinogen and clot degradation and therefore increase the shelf-life stability and the longevity and integrity of the clot by preventing premature fibrinolysis [11].

Previously, the only study [13] comparing EVICEL Fibrin Sealant (Human) and TISSEEL Fibrin Sealant was a biomechanical performance comparison regarding strength of repair following the utilization of the two products following the suture repair of experimentally transected nerves. Nerve sections treated with EVICEL, DuraSeal polyethylene glycol sealant (Confluent Surgical, Inc., Waltham, Massachusetts, USA) demonstrated significantly greater resistance to gapping than the control group (no treatment; P < 0.01 for all comparisons); no differences were observed between active treatments.

No other published studies to date have compared the physicochemical properties of fibrin clots formed following application of EVICEL Fibrin Sealant (Human) with those formed with other commercially available fibrin sealants. The present study was therefore designed to compare the mechanical, kinetic, and biochemical properties of fibrin clots formed with EVICEL and TISSEEL.
properties of the fibrin clots produced using EVICEL Fibrin Sealant (Human) and TISSEEL Fibrin Sealant. This study was funded by OMRIX Biopharmaceuticals R&D, Israel; editorial support for this manuscript was funded by ETHICON, Inc. The authors were not compensated and retained full editorial control over the content of the manuscript.

Methods

Preparation of fibrin sealants

EVICEL Fibrin Sealant (Human) was supplied as a kit consisting of the following two separate components: one vial each of BAC2 (55–85 mg/ml fibrinogen) and thrombin (800–1200 IU/ml human thrombin) frozen solutions [10]. These components were thawed prior to use.

TISSEEL Fibrin Sealant was supplied as a kit consisting of two prefilled syringes that contained a sealer protein solution (67–106 mg/ml fibrinogen and 2250–3750 IU/ml synthetic aprotinin) and a thrombin solution [400–625 IU/ml thrombin (human) diluted in calcium chloride] [12].

Young modulus and tensile strength testing

The Young modulus (also known as the modulus of elasticity, a measure of the force required to change the shape of a fibrin clot by a predefined amount) and the tensile strength (the maximal force applied prior to failure/breakage) of fibrin clots were measured using a motor-driven tension and compression tester (LF Plus Tensile Machine, Lloyd Instruments, Fareham, UK), using a method similar to that previously reported by Velada and colleagues [14].

Fibrin clots for testing were created with EVICEL Fibrin Sealant (Human) or TISSEEL Fibrin Sealant using casts designed for testing in an elongation test. Each cast comprised two conical parts. The upper part was mounted with its narrow end facing downwards on top of the lower part with its narrow end facing upwards, forming a dumbbell shape. The aluminum casts were coated with Vaseline for sealing. The casts were placed on a hard surface lubricated with Vaseline. The two solutions for each fibrin sealant were drawn into separate 5-ml syringes and then injected together into the casts. The casts were filled to the top with approximately 1.5 ml of combined solutions and then incubated at 37°C for 30 min to allow adequate polymerization. Three batches from each kit were tested at a 1:20 dilution, while the TISSEEL Fibrin Sealant samples were tested at a 1:20 dilution and undiluted. Three batches from each kit were analyzed, and mean values of factor XIII concentrations were calculated. The lower limit of quantitation of the testing kit was 0.2 IU/ml.

Factor XIII activity

The presence of factor XIII activity in the respective fibrinogen components of EVICEL Fibrin Sealant (Human) and TISSEEL Fibrin Sealant was analyzed using a Berichrom F XIII kit (Dade Behring, Marburg, Germany). The EVICEL Fibrin Sealant (Human) samples were tested at a 1:20 dilution, while the TISSEEL Fibrin Sealant samples were tested at a 1:20 dilution and undiluted. Three batches from each kit were analyzed, and mean values of factor XIII concentrations were calculated. The lower limit of quantitation of the testing kit was 0.2 IU/ml.

Statistical analysis

Calculated mean Young modulus and tensile strength values and mean values for parameters obtained from the TEG test for EVICEL Fibrin Sealant (Human) and TISSEEL Fibrin Sealant were compared using a two-sample, two-tailed, t-test with a significance level of 0.05.
Results
Young modulus and tensile strength testing
The mean Young modulus of the fibrin clots produced using EVICEL Fibrin Sealant (Human) was significantly higher than that of those produced using TISSEEL Fibrin Sealant (Table 1; Fig. 1). In addition, the mean tensile strength of the EVICEL Fibrin Sealant (Human) fibrin clots was approximately five times higher than that of the fibrin clots produced with TISSEEL Fibrin Sealant (Table 1).

Thromboelastography
The TEG analysis results are shown graphically in Fig. 2. The time to initial fibrin clot formation (R) and time to the predefined level of fibrin clot formation (K; for the samples diluted 1 : 20) were numerically shorter for EVICEL Fibrin Sealant (Human) compared with TISSEEL Fibrin Sealant, although these differences did not reach statistical significance (Table 2). In addition, the mechanical values measured by the TEG [maximum amplitude (MA), clot strength (G), and elasticity (E)] were numerically higher with EVICEL Fibrin Sealant (Human) than with TISSEEL Fibrin Sealant. Notably, significantly higher angle values were obtained with EVICEL than with TISSEEL Fibrin Sealant ($P < 0.0001$).

Factor XIII activity
The mean concentration of factor XIII in the fibrinogen component (tested at a 1 : 20 dilution) of EVICEL Fibrin Sealant (Human) was 9 IU/ml. For the fibrinogen component of TISSEEL Fibrin Sealant, no factor XIII was detectable at either the 1 : 20 dilution or in undiluted fibrinogen.

Discussion
Evaluations of mechanical, kinetic, and biochemical properties demonstrated that fibrin clots formed with EVICEL Fibrin Sealant (Human) have a higher resistance to stretching and are more capable of maintaining their structure against applied force than those formed with TISSEEL Fibrin Sealant. Moreover, the greater tensile strength of the EVICEL Fibrin Sealant (Human) fibrin clots indicates that those clots can withstand greater mechanical forces before yielding than the fibrin clots formed with TISSEEL Fibrin Sealant, which translates to stronger and more stable clots that are clinically less likely to give way to bleeding. Comparison of kinetic and mechanical properties using TEG analysis indicated that EVICEL Fibrin Sealant (Human) also facilitates more rapid development of fibrin clots than TISSEEL Fibrin Sealant.

The undetectable factor XIII concentrations in the TISSEEL Fibrin Sealant samples (tested at both a 1 : 20 dilution and undiluted) during direct assay indicated that there was very little covalent factor XIII-associated cross-linking in the TISSEEL Fibrin Sealant. Because the fibrin sealants contained comparable amounts of fibrinogen, the superior clot strength and resilience obtained with EVICEL Fibrin Sealant

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean (SD) Young modulus and tensile strength values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>EVICEL ($n = 15$)</td>
</tr>
<tr>
<td>Young modulus (kPa)</td>
<td>38 (5)*</td>
</tr>
<tr>
<td>Tensile strength (kPa)</td>
<td>135 (15)*</td>
</tr>
</tbody>
</table>

SD, standard deviation. *$P < 0.001$ vs. TISSEEL Fibrin Sealant.
(Human) relative to TISSEEL Fibrin Sealant may therefore be largely attributed to the factor XIII activity.

Fibrinolysis and coagulation are greatly affected by the activity of factor XIII, which is the final enzyme activated in the coagulation cascade [15]. Following activation by thrombin, factor XIII leads to the formation of covalent cross-links between fibrin polymers, which strengthen fibrin clots [16]. In the absence of factor XIII, such cross-linking does not occur, resulting in a weaker, softer clot [17]. This evidence suggests that the presence of factor XIII in fibrin sealants may contribute to their clinical efficacy, especially when considered in the context of patients with low physiologic levels of factor XIII [15]. In fact, Dickneite and colleagues [17] found that fibrin sealants lacking detectable factor XIII were associated with soft and weak fibrin clots, as similarly demonstrated in the current study. In addition, Kheirabadi and colleagues [18] suggested that fibrin sealants with higher factor XIII may be associated with stronger fibrin clots than those with low levels of factor XIII.

Dickneite and colleagues [17] highlighted that the TISSEEL VH kit (an earlier version of TISSEEL: Vapor Heated, Solvent/Detergent Treated) does not contain detectable factor XIII, whereas the fibrin sealant kits sold in Europe and Japan by the same company [e.g. Tissucol and Tissucol Duo S (frozen)] contain approximately 10 IU/ml factor XIII [16]. Because manufacturing is performed using a similar process with plasma cryo-precipitate, it would appear that unlike Tissucol, TISSEEL Fibrin Sealant is not supplemented with plasma-derived factor XIII.

Whereas the current study provides evidence that may translate into positive clinical outcomes, there are currently no published studies of fibrin sealants showing a correlation between in-vitro product characteristics and clinical performance, nor are there any head-to-head clinical trials that might be extrapolated to confirm these in-vitro results. Additional rigorous studies are therefore necessary to explore and resolve these issues more fully.

In conclusion, the results of the present study demonstrate that, in vitro, EVICEL Fibrin Sealant (Human) produces a stronger and more resistant fibrin clot than TISSEEL Fibrin Sealant, which is likely the result of the higher factor XIII activity associated with the fibrinogen component of EVICEL Fibrin Sealant (Human).

### Acknowledgements

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### Disclosures

This study was funded by OMRIX Biopharmaceuticals R&D, Israel. W.L.H. is on a speaker’s bureau for Johnson & Johnson but has received no compensation for that work. I.N. and R.M. are employees of OMRIX Biopharmaceuticals.

### References


### 2.2 Preparation Prior to Application

Once thawed, use the components of EVICEL® (BAC2 and Thrombin), within 30 days of storage at room temperature, or within 30 days if stored refrigerated. Do not refrigerate EVICEL® after storage at room temperature. Discard unused product after 24 hours if stored at room temperature or after 30 days if stored refrigerated. Do not use after the expiration date stated on the box, or after 30 days if stored refrigerated.

#### Dose and Strengths

EVICEL® is supplied as a kit consisting of two separate packages:

- A package containing one vial each of BAC2 (55-85 mg/ml fibrinogen) and Thrombin (800-1200 IU/ml human thrombin) frozen solutions.
- A spray application device.

#### Dosage and Administration

**EVICEL is a fibrin sealant which must be used in conjunction with a Spray Engagement Device supplied. EVICEL forms a transparent layer on application through which surgical and cautery, prior to the application of EVICEL®.**

The distance between the components of EVICEL® (BAC2 and Thrombin) in one of the following:

- 2°C to 8°C (refrigerator); vials thaw within 1 day; or
- 2°C to 37°C; vials thaw within 10 minutes and must not be left at this temperature for more than 30 minutes. Do not use if temperature has not reduced to ≤37°C.

### 3. DOSAGE FORMS AND STRENGTHS

The different EVICEL® dosage forms include the following sizes (Table 2):

<table>
<thead>
<tr>
<th>Size</th>
<th>Size with Layer of EVICEL®</th>
<th>Thickness</th>
<th>Area of Coverage with 1 Layer of EVICEL®</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0 ml</td>
<td>0.5 mm</td>
<td>1 mm</td>
<td>25 cm²</td>
</tr>
<tr>
<td>5.0 ml</td>
<td>1.0 mm</td>
<td>1 mm</td>
<td>50 cm²</td>
</tr>
<tr>
<td>10.0 ml</td>
<td>5.0 mm</td>
<td>1 mm</td>
<td>100 cm²</td>
</tr>
<tr>
<td>5.0 ml</td>
<td>0.1 mm</td>
<td>3 mm</td>
<td>25 cm²</td>
</tr>
<tr>
<td>5.0 ml</td>
<td>1.5 mm</td>
<td>3 mm</td>
<td>50 cm²</td>
</tr>
<tr>
<td>10.0 ml</td>
<td>7.5 mm</td>
<td>3 mm</td>
<td>100 cm²</td>
</tr>
</tbody>
</table>

### 3.2 Application Techniques

#### Application by Dripping

- a) Connect the luer-lock of the air tube (with the 0.2 μm filter) to a pressure regulator to administer EVICEL®. This event appears to be related to the use of the spray device employing pressure to meter the dose of EVICEL®. Air or gas embolism has occurred with the use of spray devices employing pressurized solutions, such as ethylene oxide gas, carbon dioxide, and in close proximity to the tissue surface.

- b) Connect the luer-lock of the air tube (with the 0.2 μm filter) to a spray application device.

#### Application by Spray

- a) The tip of the spray device is placed on the surface of the tissue to be treated, at a distance of 10 to 15 cm from the bleeding site or incision.

- b) The spray device is operated at the recommended pressure by the application device manufacturer. The distance between the components of EVICEL® (BAC2 and Thrombin) in one of the following:

<table>
<thead>
<tr>
<th>Size</th>
<th>Size with Layer of EVICEL®</th>
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<td>1.0 mm</td>
<td>1 mm</td>
<td>50 cm²</td>
</tr>
<tr>
<td>10.0 ml</td>
<td>5.0 mm</td>
<td>1 mm</td>
<td>100 cm²</td>
</tr>
</tbody>
</table>

### 4. ADVERSE REACTIONS

The most serious adverse events reported during clinical trials were hypotension, systemic inflammatory response syndrome/vascular collapse, drug reaction, allergic reaction, isotretionocytosis, thrombocytopenia, and other hematologic disorders. The most common adverse events included:

- Bradycardia, nausea, hypotension, hypoxia, tachycardia, pyrexia, graft infection, vascular graft occlusion, back pain, wound Healing Abnormal, Hypertension, Bradycardia, Nausea, Hyperglycemia, Hypotension, Tachycardia.

### 5.0. DOSAGE FORMS AND STRENGTHS

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### 6. ADVERSE REACTIONS

The most serious adverse events reported during clinical trials were hypotension, systemic inflammatory response syndrome/vascular collapse, drug reaction, allergic reaction, isotretionocytosis, thrombocytopenia, and other hematologic disorders. The most common adverse events included:

- Bradycardia, nausea, hypotension, hypoxia, tachycardia, pyrexia, graft infection, vascular graft occlusion, back pain, wound Healing Abnormal, Hypertension, Bradycardia, Nausea, Hyperglycemia, Hypotension, Tachycardia.

### 7. DRUG INTERACTIONS

No drug interactions are known.
HIV-1: Human Immunodeficiency Virus Type 1
HAV: Hepatitis A Virus
EMCV: Encephalomyocarditis virus

Table 4: Results of virus removal/inactivation in validation studies

<table>
<thead>
<tr>
<th>Type of Virus</th>
<th>HI Reduction</th>
<th>BVV Reduction</th>
<th>EMCV Reduction</th>
<th>CPV Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>&gt;10.63</td>
<td>&gt;10.18</td>
<td>&gt;4.74</td>
<td>&gt;9.72</td>
</tr>
<tr>
<td>BVDV</td>
<td>6.37</td>
<td>6.95</td>
<td>5.85</td>
<td>6.37</td>
</tr>
<tr>
<td>PRV</td>
<td>6.37</td>
<td>6.95</td>
<td>5.85</td>
<td>6.37</td>
</tr>
<tr>
<td>EMCV</td>
<td>6.37</td>
<td>6.95</td>
<td>5.85</td>
<td>6.37</td>
</tr>
<tr>
<td>HAV</td>
<td>6.37</td>
<td>6.95</td>
<td>5.85</td>
<td>6.37</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

No differences in safety or effectiveness were observed between the elderly and younger patients.

11 DESCRIPTION

EVICEL® is manufactured from pooled human plasma. EVICEL® is provided as a single use kit consisting of two packages. One package contains one vial of Biological Activated Clotting Site (BAC2) and one vial of Thrombin. The other package is a sterile spray application device. The two components must be reconstituted and mixed according to the directions provided. The thrombin solution is reconstituted with water before mixing with the BAC2 column. After mixing, the preparation is subsequently treated by pasteurization.

9.2 Limitations

Limited data are available to support the safety and effectiveness of EVICEL® in children under 12 years of age. There are no data available on the safety and effectiveness of EVICEL® in children weighing less than 15 kg.

3.2 Indications

EVICEL® is indicated for the management of dieback of the fibrin clot resulting from partial hepatectomy, and for the control of surgical bleeding during liver, pancreatic, stomach, and colorectal surgery.

12 CLINICAL PHARMACOLOGY

12.1 Pharmacokinetics

Intramuscular administration of EVICEL® does not result in detectable plasma concentrations of EVICEL® or its components.

12.2 Pharmacodynamics

Hemostasis at 10 min 66 (91.7%) 48(70.6%) 1.18 1.04; 1.36

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis

No differences in safety or effectiveness were observed between the elderly and younger patients.

15.1 Mutagenesis

15.2 Animal reproduction

Animal reproduction studies have not been conducted with EVICEL®. It is not known whether EVICEL® is capable of causing fetal harm when administered to pregnant women. Because EVICEL® is for topical use only and intravascular administration is contraindicated, no carcinogenic or mutagenic potential of EVICEL® due to the human origin of both thrombin and fibrinogen contents.

17 PATIENT COUNSELING INFORMATION

The effect of EVICEL® on fertility has not been evaluated.

11.2 Neutrophilia

Studies performed in bacteria to determine mutagenicity were negative for Thrombin-alone, soiling of Thrombin-alone and EVICEL® as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal or intra-abdominal surgery. No increases in the number of runts. No embryo-fetal adverse effects were observed at 100-fold (TnBP, 7500 μg/kg/day) the human dose.

11.2.2 Fibrinogen

EVICEL® as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal or intra-abdominal surgery.

5.3 minutes for EVICEL® versus 7.7 minutes for control; one-sided p < 0.001). Hemostasis at 5 minutes for Thrombin and Thrombin-alone (5.3 minutes for EVICEL® versus 7.7 minutes for control; one-sided p < 0.001).

20.2.3 Carcinogenesis

No differences in safety or effectiveness were observed between the elderly and younger patients.

20.4 Mutagenesis

Potential of EVICEL® due to the human origin of both thrombin and fibrinogen contents.

20.5 Animal reproduction

Because EVICEL® is for topical use only and intravascular administration is contraindicated, no carcinogenic or mutagenic potential of EVICEL® due to the human origin of both thrombin and fibrinogen contents.

20.6.2 Fibrinogen

EVICEL® has been classified as non-irritant in the Primary Cutaneous Irritation Test and the Draize Skin Irritation Test. EVICEL® has been classified as non-irritant in the Primary Cutaneous Irritation Test. No differences in safety or effectiveness were observed between the elderly and younger patients.

20.6.3 Thrombin

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