Randomized, Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Fibrin Sealant VH S/D 4 s-apr (Artiss) to Improve Tissue Adherence in Subjects Undergoing Rhytidectomy

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Randomized, Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Fibrin Sealant VH S/D 4 s-apr (Artiss) to Improve Tissue Adherence in Subjects Undergoing Rhytidectomy

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Clinical Trial Registration:
This trial was registered with ClinicalTrials.gov (Identification No. NCT00999141) (http://www.clinicaltrials.gov/ct2/show/NCT00999141).

Abstract
Background: Suction drains are commonly placed after rhytidectomy to avoid seroma formation that may result from dead spaces between skin layers. Fibrin sealants promote tissue adherence by crosslinking with extracellular matrix proteins, which may reduce the dead space under skin flaps.
Objectives: The authors evaluate the safety and efficacy of the fibrin sealant (FS) VH S/D 4 s-apr (Artiss; Baxter Healthcare Corp, Deerfield, Illinois), added to standard-of-care (SoC) treatment, in improving flap adherence and reducing dead space in patients undergoing rhytidectomy.
Methods: Patients with planned facial rhytidectomy were enrolled in this phase 3, prospective, controlled, randomized, patient-blinded, multicenter trial. They received SoC treatment on 1 side of the face and adjunctive FS VH S/D 4 s-apr on the other.
Results: Seventy-five patients completed the trial. The mean (SD) drainage volume was 7.7 (7.4) mL from the sides treated with sealant and 20.0 (11.3) mL from the SoC-only sides (P < .0001). Rates of hematoma and seroma were similar for the 2 treatments, as were changes in postoperative skin sensitivity. Adverse events generally were mild; 2 serious adverse events were reported (wound abscess, dehydration).
Conclusions: Adjunct use of FS VH S/D 4 s-apr in rhytidectomy was proven safe in this study. It significantly reduced drainage volumes without increasing the incidence of hematoma or seroma, which suggests that it eliminates dead space through improved flap adherence.

Level of Evidence: 2

Keywords
rhytidectomy, fibrin sealant, tissue adherence, facial surgery

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eliminate the dead space, thereby limiting the amount of fluid collected from drains placed for rhytidectomy may serve as a surrogate marker of tissue adherence. Hematoma is a complication resulting from rhytidectomy that reportedly occurs in 0.2% to 8.0% of women and 7.9% to 12.9% of men who undergo this surgery. Although small hematomas can be treated by drainage through aspiration or incision, large expanding hematomas may require reoperation to evacuate the blood and cauterize the bleeding vessels. Seroma is another complication resulting from rhytidectomy. Various factors contribute to the secretion and accumulation of fluids and subsequent seroma formation. These include surgical manipulation of underlying tissues, surgical creation of dead space during skin-flap elevation and attachment, and disruption of the lymphatic systems in the temporal, cheek, and neck regions. The sequelae associated with seroma may include infections, dehiscence, and skin-flap necrosis, all of which can significantly affect morbidity and recovery rates.

Fibrin sealants are utilized in a variety of surgical procedures for sealing, hemostasis, and adherence purposes. In plastic and reconstructive surgery, these sealants are used to attach split-thickness skin grafts to wound beds and to reduce bleeding and seroma formation. Thus, products of this type have the potential to improve healing and reduce the complications associated with rhytidectomy. Fibrin sealant with 4 U/mL human thrombin, vapor-heated, solvent/detergent-treated synthetic aprotinin (FS VH S/D 4 s-apr) (Artiss fibrin sealant [human]; Baxter Healthcare Corp, Deerfield, Illinois) is a dual-component (fibrinogen and thrombin) product for topical use. This product was initially approved by the United States Food and Drug Administration for topical use in the treatment of bleeding associated with surgical and nonsurgical procedures. Its use has been expanded to include adjuvant topical application to surgical wounds and incisions to enhance healing and reduce the incidence of complications such as infection, closure failure, seroma, and hematoma formation. The objective of the present study was to evaluate and confirm the safety and efficacy of this fibrin sealant in patients undergoing rhytidectomy.

METHODS

Patients

Healthy patients aged 18 to 75 years with plans for full rhytidectomy were eligible to participate in the trial. Abbreviated or modified facelift procedures were not permitted, nor were concurrent facial surgery or procedures to other areas of the body. Additional key exclusion criteria included previous rhytidectomy surgery, a known bleeding or coagulation disorder, concurrent treatment with anticoagulants, or use of aspirin within 7 days prior to surgery. Written informed consent was obtained from all patients prior to the initiation of any study-related procedures.

Study Design

This phase 3, prospective, controlled, randomized, multicenter clinical trial was conducted between September 2009 and December 2009. Seven study sites in the United States participated in the trial. The study protocol and informed consent form were reviewed and approved by the centralized Western Institutional Review Board (Olympia, Washington) prior to initiation of the study. In addition, they were approved by the Institutional Review Board at the University of Texas Southwestern Medical Center at Dallas for 1 study site. The trial complied with the principles of the International Conference on Harmonization Good Clinical Practice and the Declaration of Helsinki.

One side of each patient’s face was treated with a single dose of FS VH S/D 4 s-apr intraoperatively as an adjunct to the standard of care (SoC; routine procedure without application of FS VH S/D 4 s-apr), and the other side received SoC only. Thus, each patient served as her or his own control. Determination of the side of the face that was to receive FS VH S/D 4 s-apr with SoC was established by a predefined randomization process. Patients were aware that both study product and placebo treatments would be administered, but they were blinded throughout the entire study as to which side of their face received each treatment.

Although varying surgical techniques were performed to achieve complete rhytidectomy (short or standard scar approaches were permitted, as was plication or elevation of the SMAS), all surgeries in this study involved full undermining of the skin and manipulation of the soft tissue. Furthermore, the same surgical procedure was performed on both sides of the face for each patient. The following procedures were not permitted: minimal-access cranial suspension, thread lifts, minimal undermining procedures, deep-plane facelifts, and concomitant facial, nasal, or neck liposuction. Pressure dressings were also not allowed. Symmetrical fine liposuction of the neck/jowls was permitted at the discretion of the investigator and was documented. Chin and/or cheek implants were also allowed and documented. Only the principal investigator was permitted to carry out surgical procedures. Most standard surgical techniques used to achieve hemostasis
cautery, direct pressure, and gauze pads soaked with epinephrine) were permitted.

Prior to the end of surgery but before the application of FS VH S/D 4 s-apr, a flat, 7-mm Blake silicone drain (Ethicon, Inc; Somerville, New Jersey) was placed in the lower part of the neck on each side of the face (Figure 1A). The drains were removed 24 ± 4 hours (trial day 1) after completion of the surgery, or later at the discretion of the surgeon. Fluids from each drain were transferred to separate, standardized graduated cylinders for accurate measurement of drainage volume (Figure 1B).

**Product Administration**

FS VH S/D 4 s-apr was applied to the subcutaneous plane in both the neck and facial area of the side assigned to receive experimental treatment. The dosing volume of FS VH S/D 4 s-apr ranged from 0.02 to 0.04 mL/cm². The product was applied to the wound bed using a side-to-side painting motion to achieve a single, thin layer. During application, gentle pressure was applied at the midline of the neck to prevent cross-contamination of the control test site. The flap was held in place for 3 minutes.

**Outcome Measures**

The primary efficacy end point was the total drainage volume collected from each side of the face at 24 ± 4 hours postoperatively. The primary safety end point was the incidence of adverse events (AE) related to FS VH S/D 4 s-apr throughout the study. Safety was evaluated on day 0 (day of surgery) and on postoperative days 1, 3, 7, and 14. Secondary end points included the occurrence of hematoma and seroma on each side of the face, comparison of edema between the sides of the face, changes in skin sensitivity from baseline on each side of the face, patient treatment preference, and patient assessment of numbness (on a 10-point scale, with 10 denoting the greatest numbness). The investigators inspected the operated areas for hematoma and seroma after surgery on day 0 (encompassing

![Figure 1. Drainage collection procedure. (A) Flat 7-mm Blake silicone drains were placed in the lower part of the neck. The drains were removed 24 hours postoperatively. (B) The contents of each drain were transferred to graduated cylinders for measurement.](image-url)
events that occurred on the day of surgery, but after the surgical procedure) and at all postoperative visits (postoperative days 1, 3, 7, and 14). Any occurrence of hematoma or seroma on days that were not prescheduled trial visits was also reported. Multiple hematomas and seromas occurring in the same patient were documented separately. If a hematoma or a seroma was treated, the type of intervention and the volume of fluid drained were recorded. Hematomas or seromas located on the midline of the face and/or neck were assessed as 2 separate findings (1 on each side of the face).

The investigators examined patients to determine the extent of edema on both sides of the face. Skin sensitivity was assessed using a Semmes-Weinstein Monofilament set. This test was administered at the middle of the imaginary line running between the tragus and the mouth commissure, and sensitivity was defined as the smallest monofilament size felt by the patient. Patient preference was assessed by asking patients, in an open and holistic manner, which side of their face they preferred (left, right, or no preference). Patients were given a number of options to support their choice: better skin sensation, less numbness, looks better, less bruising, less swelling, less pain, less itching, less tingling, less feeling of “pins and needles,” and other (free-text section). Patients were asked in a written questionnaire to choose all reasons that applied to their situation. They were also asked to assess their degree of numbness using a 10-point scale.

Statistical Analyses

We calculated that a sample size of 75 would provide 91% power to detect a mean (SD) difference in drainage volume between the 2 sides of the face of at least 13.7 (34.5) mL. The efficacy analysis set comprised all randomized subjects who underwent facial rhytidectomy, received SoC or SoC plus FS VH S/D 4 s-apr, and provided data for the primary efficacy end point. The safety analysis set included all subjects who underwent facial rhytidectomy and received SoC or SoC plus FS VH S/D 4 s-apr.

Statistical significance for the primary efficacy end point (total drainage volume collected from each side of the face at 24 ± 4 hours postoperatively) was calculated using a 2-sided paired t test. Utilizing a 2-sided McNemar’s test of paired proportions, the number of patients with hematoma/seroma on the SoC-only side of the face exclusively was compared with the number of patients with hematoma/seroma on the FS VH S/D 4 s-apr side of the face exclusively. A 95% confidence interval (CI) around the difference in paired proportions was computed based on Newcombe’s method. The proportion of patients deemed to have less edema on the side treated with FS VH S/D 4 s-apr and the proportion deemed to have less edema on the SoC-only side were computed and presented with a McNemar 95% CI. Data were analyzed as observed, with no imputation for missing data.

RESULTS

Patients

Of the 79 patients enrolled in the trial, 4 did not complete it (2 screening failures; 2 withdrawals of consent prior to surgery). Of the 75 patients who completed the trial, 71 (95%) were women and 4 (5%) were men. The mean (SD) age was 54.4 (7.4) years (range, 40-71 years), and 74 (99%) of patients were white. The efficacy and safety analysis sets comprised the 75 patients who completed the study.

Efficacy

Drainage Volumes

A statistically significant difference in the 24-hour postoperative drainage volumes was observed, favoring the side of the face treated with FS VH S/D 4 s-apr (P < .0001). The mean (SD) drainage volume was 7.7 (7.4) mL on that side of the face as opposed to 20.0 (11.3) mL on the side treated with SoC only. The mean (SD) difference in the 24-hour postoperative drainage volumes between the 2 sides of the face was 12.3 (11.4) mL, in favor of the side treated with FS VH S/D 4 s-apr. Although overall drainage propensity varied among the study sites, volumes were consistently lower on the sides that received FS VH S/D 4 s-apr treatment (Table 1 and Figure 2).

Hematoma/Seroma

Five patients experienced a total of 7 hematoma/seroma events on the side of the face treated with FS VH S/D 4 s-apr (1 hematoma in 1 patient; 6 seromas in 4 patients; Table 2). On the SoC-treated sides of the face, a total of 8 events occurred in 8 patients (4 hematomas; 4 seromas). Two of the 75 patients (3%) experienced hematoma/seroma exclusively on the side treated with FS VH S/D 4 s-apr, and 5 (7%) patients experienced hematoma/seroma exclusively on the side treated with SoC only (Table 2). The difference was not statistically significant (.040; 95% CI, -0.039 to 0.125; P = .257). In 3 (4%) of the 75 patients, hematoma/seroma occurred on both sides of the face. Most patients (65 of 75; 87%) did not experience hematoma/seroma on either side of the face during the trial.

Four patients required treatment for hematoma/seroma events on the FS VH S/D 4 s-apr–treated side of the face. For these individuals, the mean (SD) total volume of aspiration was 5.3 (5.0) mL. Seven patients required treatment for events on the SoC-only side of the face. For these individuals, the mean (SD) total volume of aspiration was 6.7 (4.7) mL.

Early clinical results are shown in Figures 3 and 4.

Edema

Significantly more patients had less edema on the side treated with FS VH S/D 4 s-apr at every trial visit (Figure 5).
Adjustments for multiplicity yielded statistically significant differences for all trial visits except postoperative day 14.

**Skin Sensitivity**
The data pertaining to skin sensitivity varied greatly and thus precluded analysis of differences between the treatments.

**Patient Treatment Preference**
At each trial visit, the majority of patients stated a preference for the side treated with FS VH S/D 4 s-apr (Figure 6). Common reasons for preferring either treatment were less swelling, better appearance, and less bruising. In addition, patients who preferred the FS VH S/D 4 s-apr–treated side reported experiencing less pain on that side.

**Numbness**
At each postoperative visit, patients reported more numbness on the SoC-treated side of the face; however, the differences between treatments were small.

**Safety**
Two serious AE (SAE) were reported. One patient experienced dehydration, and another had a wound abscess with methicillin-resistant *Staphylococcus aureus* on the side treated with FS VH S/D 4 s-apr, which occurred 14 days postoperatively. Although the latter SAE was initially considered related to treatment, it was later deemed unrelated because of its late onset in relation to product application. Of the remaining 35 AE, all were mild in severity except for a case of corneal abrasion and a case of procedural pain, which were considered moderate in severity. Two of the non-SAE were considered related to treatment: 1 patient had mild cellulitis on the side of the face treated with FS VH S/D 4 s-apr (14 days postoperatively), and 1 patient had mild seroma on postoperative day 1. A total of 12 facial AE in 11 (15%) patients occurred exclusively on the sides that received SoC only. A total of 11 facial AE in 6 (8%) patients occurred exclusively on the side treated with FS VH S/D 4 s-apr. Six facial AE in 6 (8%) patients occurred on both sides of the face.

**DISCUSSION**
The present study, which utilized drainage volume as a surrogate marker for dead-space prevalence, suggests that improved flap adherence can be obtained by applying FS VH 4 U/mL human thrombin, vapor-heated, solvent/detergent-treated synthetic aprotinin + standard-of-care treatment. It is generally accepted that drains may be removed when the total drainage volume is ≤30 mL (or by inference, ≤15 mL per side of the face) in a 24-hour period. The use of FS in plastic surgery procedures may eliminate dead space under the skin flap, leading to a reduction in drainage volume and thereby avoiding the need for drains. Our results suggest that the use of FS VH S/D 4 s-apr reduced the mean drainage volume to a level well below the threshold for drain justification (30 mL, or 15 mL per side). In our trial, 91% of patients had a drainage volume of ≤15 mL from the side of the face treated...
with FS VH S/D 4 s-apr in the first 24 hours postoperatively, whereas only 43% of patients had a drainage volume of ≤15 mL on the SoC-only side. Of the 43 patients whose drainage volume from the SOC-only side was ≥15 mL 24 hours postoperatively, the corresponding volume for the side treated with FS VH S/D 4 s-apr was ≤15 mL for 38 of them. These results imply that adjunct use of FS VH S/D 4 s-apr would preclude the need for drains in 88% of patients who meet the criteria for drain placement under SoC.

The rates of hematoma were similar for the 2 treatment protocols. The rates of seroma were also similar, which suggests that the reduction in drainage in the 24 hours immediately following surgery with adjunct FS VH S/D 4 s-apr was achieved without a coincident increase in the incidence of seroma or hematoma. Of the seromas that required aspiration, the mean volume of aspirated fluid was lower for those that occurred on the side treated with FS VH S/D 4 s-apr. These findings imply that FS VH S/D 4 s-apr reduces fluid accumulation by eliminating dead space through improved flap adherence, rather than merely preventing fluid from reaching the drain. The relatively high incidence of hematoma and seroma observed in our trial may be attributable to the structure of the study. The rigorous reporting of safety data that is common in clinical trials such as ours produces more accurate assessments of AE than do data from observational studies that use retrospective chart reviews. As expected, very few patients in our trial were men (4 of 75; 5%), which precluded a subgroup analysis of the rate of hematoma/seroma by sex.

Although the FS VH S/D 4 s-apr–treated sides of the face had less edema than the SoC-treated sides, the investigators were not blinded to treatment in this trial, which could have influenced the assessments. Nevertheless, this finding lends further credence to the hypothesis that adjunct use of FS VH S/D 4 s-apr reduces fluid accumulation by eliminating dead space through improved flap adherence, especially because it is consistent with patient-reported preferences (all patients were blinded to treatment). At all trial visits, the majority of patients reported preference for the side of the face treated with FS VH S/D 4 s-apr. Although patients reportedly had greater numbness on the side treated with SoC alone, differences between the numbness levels reported for the SoC sides of the face as compared with the FS VH S/D 4 s-apr–treated sides were small. Because of high variance among the data, we were unable to detect a difference in skin sensitivity between the 2 sides of the face.

The use of FS VH S/D 4 s-apr was associated with a good safety profile in this trial. These results are consistent with those observed in previous clinical trials of FS VH S/D 4 s-apr, including a study conducted in burn patients.

**CONCLUSIONS**

The findings in this study suggest that adjunct use of FS VH S/D 4 s-apr in rhytidectomy surgery is safe and, compared with SoC alone, significantly reduces the volume of drainage (a surrogate marker of improved flap adherence) in the first 24 hours postoperatively. Moreover, the results

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**Figure 2.** Drainage volumes (mL) 24 hours postoperatively for each patient, according to type of treatment. FS VH S/D 4 s-apr, fibrin sealant with 4 U/mL human thrombin, vapor-heated, solvent/detergent-treated synthetic aprotinin; SoC, standard of care.

**Table 2. Hematoma/Seroma Incidence**

<table>
<thead>
<tr>
<th></th>
<th>FS Side</th>
<th>SoC Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with hematoma, n</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hematomas, n</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hematomas requiring aspiration, n</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Mean volume aspirated, mL (SD; range)</td>
<td>1.0</td>
<td>4.7 (2.4; 2.5-8.0)</td>
</tr>
<tr>
<td>Patients with seroma, n</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Seromas, n</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Seromas requiring aspiration, n</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mean volume aspirated, mL (SD; range)</td>
<td>6.7 (5.1; 3.0-12.5)</td>
<td>9.4 (6.3; 4.7-16.5)</td>
</tr>
</tbody>
</table>

FS, fibrin sealant with 4 U/mL human thrombin, vapor-heated, solvent/detergent-treated synthetic aprotinin + standard-of-care treatment; SD, standard deviation; SoC, standard-of-care treatment only.
Figure 3. (A, C, E) The 41-year-old woman shown in Figure 1 is shown 1 day after undergoing standard-of-are (SoC) rhytidectomy treatment on the left side of her face, with SoC plus adjuvant treatment with fibrin sealant on the right. (B, D, F) Seven days postoperatively.
Figure 4. (A, C, E) A 49-year-old woman, 1 day after undergoing standard-of-care (SoC) rhytidectomy treatment on the left side of her face, with SoC plus adjuvant treatment with fibrin sealant on the right. (B, D, F) Seven days postoperatively.
suggest that the need for drain placement in rhytidectomy is reduced when FS VH S/D 4 s-apr is applied. Drainage reduction was achieved without an increased incidence of hematoma or seroma, indicating that the application of FS reduced fluid accumulation by eliminating dead space through improved flap adherence.

**Disclosures**

Drs. Nguyen, Gerut, Chen, Diamond, and Hester are paid consultants; Dr. Shire is a paid consultant, lecturer, and advisory board member; and Ms. Silvati-Fidell and Drs. Desmond and Abrams are employees and stockholders of Baxter Healthcare, the manufacturer of the product discussed in this article. Prof. Rohrich is not a paid consultant for Baxter Healthcare.

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**REFERENCES**


