The classic skin-flap operation used in rhytidectomy involves undermining the skin and subcutaneous tissue to varying extents over the face, jawline, and neck. The skin flap is fashioned, rotated, and advanced in a posterocephalic direction, before being attached with key sutures. As a final step, excess skin is trimmed and the wounds are closed. The success of the procedure requires adequate adherence of the skin flap to the underlying tissue. In addition, proper management of the multiple facial layers, as well as the dead space created during surgery, is essential for the safety of the patient and the success of the procedure.1

Capillary oozing under the surgical flaps and in the wound bed is extremely common after rhytidectomy, and in most patients it manifests as ecchymosis and edema (bruising and swelling). This type of bruising cannot be
avoided even with the most meticulous surgical hemostasis or the use of occlusive dressings or drains. Small-vessel, low-pressure bleeding tends to appear in areas of loose tissue and where dead space is present. Often, these minute collections of blood originate from capillaries that do not bleed while the patient is under anesthesia. However, when patients emerge from the anesthetized state, blood pressure can increase and trigger postoperative bleeding. The resulting bruising remains visible for 2 weeks or more and in many cases is the primary reason for a delay in the patient returning to work or a normal social life.2

Fibrin sealants have been shown to enhance adherence of tissue to the wound bed,3 which may reduce ecchymosis by preventing shear irritation and minimizing the dead space under the skin where fluid can accumulate. The presence of fibrin has long been known to increase the likelihood of a successful autologous skin graft,4 and the use of fibrin sealant in infected tissue has had a positive effect on the success of skin grafts.5 Findings from recent studies suggest that the use of fibrin sealants in patients who undergo rhytidectomy is associated with reduced ecchymosis.6-8 However, it should also be noted that the use of fibrin sealants is controversial; a number of physicians have found no clinically significant difference between administration of such products and standard hemostatic procedures following facelifts.9,10

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. FS VH S/D 4 s-apr received initial US Food and Drug Administration (FDA) approval in 2008 for use in adhering autologous skin grafts to surgically prepared wound beds resulting from burns in adults and pediatric patients ≥1 year of age. Previous studies have demonstrated the effectiveness of using lower concentrations of thrombin (with slower polymerization times) for the purposes of graft or flap adherence.11-13 Products are available with higher thrombin concentrations (eg, 500 U/mL) for polymerization within seconds for hemostasis; however, for procedures involving grafts or flaps, adherence that occurs too rapidly might lead to premature attachment. The fibrin sealant used in the present study allowed the surgeon sufficient time (60 seconds) to position the skin flap optimally during the rhytidectomy procedure.

This study was designed to assess the safety and efficacy of FS VH S/D 4 s-apr for tissue adherence in patients who undergo rhytidectomy.

**METHODS**

**Patients**

Healthy patients aged 18 to 75 years with planned rhytidectomy were eligible to participate in the study. Abbreviated or modified facelift procedures were not permitted, nor was concurrent facial surgery or procedures performed on 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 preoperatively. Written informed consent was obtained from all patients prior to the initiation of any study-related procedures.

**Study Design**

This phase 2, split-faced, prospective, controlled, randomized, evaluator/patient-blinded, multicenter clinical trial was conducted from June 2008 through September 2008. Six US study sites participated in the trial. The study protocol and informed consent form were reviewed and approved by a centralized institutional review board, the Western Institutional Review Board (Olympia, Washington), prior to initiation of the study. The study complied with the International Conference on Harmonization Good Clinical Practice principles 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.

All patients received a full facelift that included extensive undermining, liposculpture, superficial musculo-aponeurotic system (SMAS) elevation, and flap fashioning. Minimal-access cranial suspension, thread lifts, minimal undermining procedures, and deep-plane facelifts were not allowed, nor was concomitant facial, nasal, or neck

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This trial was registered with ClinicalTrials.gov (Identification No. NCT00708071) on June 30, 2008 (http://clinicaltrials.gov/ct2/show/NCT00708071).

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lipsosuction. Prior to the end of surgery, a Jackson-Pratt drain (Cardinal Health, McGaw Park, Illinois) was placed on each side of the face. The drains were placed in the neck region and exited postauricularly. To ensure that no blockage of the drain occurred, after the drains were inserted, they were held out of the surgical field while the fibrin sealant was sprayed onto the wound bed. After application of the sealant, the drain was laid back down onto the wound bed and the tissue flap was positioned.

For each side of the face, the total volume of fluid that drained during the first 24 hours after surgery was recorded. The drains were removed 24 ± 4 hours after completion of the surgery, but they could remain in situ for longer, at the investigator’s discretion. Pressure dressings were not permitted. Most of the standard surgical techniques to achieve hemostasis were permitted (eg, cautery, direct pressure, gauze pads soaked with epinephrine).

Five surgeons independently evaluated the efficacy outcomes and were blinded with respect to the study sponsor, the side of the face that received FS VH S/D 4 s-apr, the side of the face that received surgery first, the time between application and photography, patient identity, study site information, and all procedural details of the facelift surgery. In addition to the 5 independent reviewers, the primary investigator at each study site designated an experienced surgeon or staff member to perform local blinded evaluations. All patients were blinded to treatment throughout the entire study.

**Product Administration**

FS VH S/D 4 s-apr was applied intraoperatively to the subcutaneous plane in the neck and facial area of the side assigned to receive FS VH S/D 4 s-apr. The dosing volume of the aerosolized sealant 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.

**Outcomes Measures**

The primary efficacy end point was the visual comparison of ecchymosis, on postoperative day 3, between the 2 sides of the face, as assessed by the 5 blinded reviewers using standard digital photographs. Photographs of the face were taken from 6 perspectives (facial views: front, left side at 90°, right side at 90°; neck views: front, 90° right, 90° left). All photographic equipment was identical for every patient and had been provided to each study site by a medical photography company (Canfield Scientific Inc, Fairfield, New Jersey). This company also set up a lighting system at each study site and comprised all patients who underwent facial rhytidectomy, received FS VH S/D 4 s-apr, and had data for the primary efficacy end point for both sides of the face. The safety analysis set included patients who underwent facial rhytidectomy and received SoC or SoC plus FS VH S/D 4 s-apr.

All secondary efficacy assessments were performed on both sides of the face on postoperative days 1, 3, 5, 7, 10, and 14. Ecchymosis was graded as follows: grade 0 = no bruising, grade 1 = barely perceivable bruising, grade 2 = present but minimal bruising, grade 3 = moderate bruising, and grade 4 = extensive bruising (blue or dark purple color; covers more than just a very small area). Each side of the face was graded separately. Postoperative edema was graded as follows: grade 1 = no edema, grade 2 = minor edema, grade 3 = moderate edema, and grade 4 = marked edema (unusual amount). The Jackson-Pratt drain (placed on each side of the face prior to the end of surgery) was used to measure the amount of fluid that accumulated under the skin flap. The fluid that drained after surgery was collected and measured at 24 hours, after which the drain could be removed at the surgeon’s discretion.

The full list of secondary efficacy end points is as follows:

- Grade of ecchymosis on postoperative day 3 as assessed by the blinded site evaluator
- Grade of ecchymosis as assessed by the 5 blinded reviewers and the unblinded investigator for each site using a modified Marchac Scale
- Visual comparison of ecchymosis between the 2 sides of the face as assessed by the 5 blinded reviewers using standard digital photographs
- Resolution of bruising (grade 0 on the modified Marchac Scale for ecchymosis)
- Resolution of swelling (grade 1 on the Marchac Scale for edema)
- Total volume of drainage 24 hours after surgery
- Occurrence of hematoma/seroma
- Assessment of facial sensation perception (performed by the investigator)
- Patient assessment of pain and numbness (on a 10-point scale)
- Patient treatment preference

The primary safety end point was the incidence of adverse events (AE) related to FS VH S/D 4 s-apr throughout the study.

**Statistical Analyses**

A sample size of 40 patients was calculated to provide > 80% power to detect a difference in rates of ecchymosis of 22%.

The efficacy analysis set included all randomized patients who underwent facial rhytidectomy, received FS VH S/D 4 s-apr, and had data for the primary efficacy end point for both sides of the face. The safety analysis set comprised all patients who underwent facial rhytidectomy and received SoC or SoC plus FS VH S/D 4 s-apr.

The proportion of patients who had less ecchymosis on the FS VH S/D 4 s-apr–treated side of the face, determined by a majority of blinded reviewers (at least 3 of 5), was compared with the proportion who had less ecchymosis on the SoC-only side, using a 2-sided McNemar test of paired proportions with 95% confidence intervals (CI). Data for patients whose visual comparison did not yield a majority ruling in favor of one treatment or the other were excluded from the analysis (possible ratings included “no ecchymosis” or “equal ecchymosis”). Differences in grades
of ecchymosis were analyzed using 2-sided Wilcoxon paired-sample tests and 90% CI with no adjustment for multiple testing. Data were analyzed as observed, with no imputation for missing data.

RESULTS

Patients

Fifty-six patients were enrolled in the study, and 45 completed it. Reasons for discontinuation were screening failure (n = 2), AE that occurred before treatment with FS VH S/D 4 s-apr (n = 1), patient request for withdrawal (n = 2), withdrawal by the study sponsor because of overenrollment (n = 2), delay in surgery (n = 1), and enrollment after the deadline (n = 1). Forty-two (93%) of the patients who completed the study were women and 3 (7%) were men. The mean age was 55.1 years (range, 43-70 years), and 42 (93%) patients were white. The efficacy and safety analysis sets comprised the 45 patients.

Efficacy

Ecchymosis

A “majority outcome” (i.e., agreement in outcome by at least 3 of the 5 blinded reviewers) was achieved for 41 patients on day 1, for 37 patients on day 5, for 40 patients on day 7, for 37 patients on day 10, and for 34 patients on day 14.

On postoperative day 3, 7 (19%) patients were deemed to have less ecchymosis on the side of the face treated with FS VH S/D 4 s-apr, and 17 (46%) patients were deemed to have less ecchymosis on the side that received SoC only (P = .064; 95% CI, 0.01-0.49). Thirteen (35%) patients were judged as having equal levels of ecchymosis on both sides of the face. Thus, a statistically significant difference in ecchymosis between the treatments was not observed visually on day 3.

Among all postoperative evaluations, the largest difference in visual-comparison outcomes occurred on day 1, when the blinded reviewers rated the SoC-only side as having less ecchymosis than the side treated with adjuvant FS VH S/D 4 s-apr (Figure 1). However, as the postsurgical time increased, the difference became less marked. From day 7 onward, the proportion of patients judged as having less ecchymosis on the side treated with FS VH S/D 4 s-apr was similar to the proportion considered to have less ecchymosis on the SoC-only side.

Assessments made by the blinded reviewers showed nominal differences in mean ecchymosis grades (modified Marchac Scale) between the 2 sides of the face, which slightly but consistently favored the SoC-only side (Figure 2). However, the only statistically significant difference was on day 3 (mean [standard deviation; SD] difference = −0.169 [0.539]; P = .027). The mean scores were highest on postoperative days 1 through 5, after which they declined over time. Although there was some variation in the scores provided by each reviewer on each postoperative assessment day, the overall trend of lower scores as the study progressed was consistent for all reviewers.

Overall, there was only slight agreement between the blinded reviewers’ assessments of FS VH S/D 4 s-apr–treated sides of the face (k coefficient = 0.139) and the SoC-only sides (k coefficient = 0.188). In general, the unblinded investigators gave lower ecchymosis grades than the blinded evaluators on each postoperative assessment day. When assessed by the investigators, mean differences in ecchymosis grades favored treatment with FS VH S/D 4 s-apr on days 1, 5, and 7. The mean difference on day 5 was statistically significant (mean [SD] difference = 0.267 [0.863]; P = .045). No differences between the

Figure 1. Visual comparisons of ecchymosis show the percentages of patients with less ecchymosis on the FS VH S/D 4 s-apr–treated side of the face (blue bars), less ecchymosis on the SoC-only side of the face (yellow bars), equal ecchymosis on both sides of the face (black bars), and no ecchymosis on either side of the face (white bars), as determined by a majority of blinded reviewers. FS, fibrin sealant with 4 U/mL human thrombin, vapor heated, solvent/detergent-treated synthetic aprotinin + SoC; SoC, standard of care.

Figure 2. Mean modified Marchac grades for ecchymosis, as determined by blinded reviewers, for the FS VH S/D 4 s-apr–treated side of the face (blue bars) and the SoC-only side (red bars) at each study visit is shown. 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.
Figure 3. Drainage volumes (mL) 24 hours after surgery for each patient, according to the type of treatment: FS VH S/D 4 s-apr + SoC (blue bars) or SoC only (red bars). 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.
2 sides of the face were observed on day 3, 10, or 14. The number of patients who achieved a modified Marchac rating of 0 (ie, resolution of ecchymosis), as assessed by both the blinded reviewers and the unblinded investigators, was too small to be evaluated statistically.

Edema
According to the blinded reviewers’ assessments, the mean Marchac grades for edema were lower for the sides treated with FS VH S/D 4 s-apr on every postoperative examination day. The difference on day 1 was statistically significant (mean [SD] difference = 0.250 [0.615]; \( P = .019 \)). For some patients, on multiple consecutive days, reviewers and investigators assigned Marchac edema grade 1 (resolution), which precludes any interpretation of a true single day of resolution.

Drainage Volume
Twenty-four hours after surgery, the mean (SD) drainage volume was 11.5 (13.7) mL from the sides of the face treated with FS VH S/D 4 s-apr and 26.8 (24.0) mL from the sides treated with SoC only (\( P < .0001 \)) (Figure 3). The median drainage volumes, respectively, were 5.0 mL (range, 0.0-50.0 mL) and 20.0 mL (range, 0.0-100.0 mL). Fifteen (33.3%) of the 45 drains remained empty on the side treated with FS VH S/D 4 s-apr (0.0 mL collected) at the 24-hour postoperative assessment, compared with only 1 (2.2%) of the 45 drains on the SoC-only side.

Hematoma/Seroma
Seven (16%) of the 45 patients had a hematoma and 2 (4%) had a seroma on the side of the face that received SoC treatment only. No patient experienced a hematoma or a seroma on the side treated with FS VH S/D 4 s-apr. The difference in the proportions of subjects experiencing hematomas/seromas exclusively on the SoC side of the face compared to exclusively on the FS VH S/D 4 s-apr side of the face was statistically significant (difference = 0.200; 95% CI = 0.08 to 0.34; \( P = .003 \)).

Two-Point Discrimination Test
The mean difference in the 2-point discrimination distances from baseline (day 0) was larger on the SoC side of the face. Substantial variability was observed on each postoperative evaluation day and for each side of the face.

Patient-Reported Outcomes
On average, patients reported lower pain levels for the FS VH S/D 4 s-apr–treated side of the face at each postoperative evaluation (Figure 4); however, the differences between treatments were not statistically significant. Patients also reported lower levels of numbness for the side treated with FS VH S/D 4 s-apr on days 1, 5, 7, and 10. With respect to treatment preference, the majority of patients preferred FS VH S/D 4 s-apr on days 3, 5, and 7 and SoC alone on days 1, 10, and 14 (Figure 5).

Clinical results from postoperative days 1 and 7 are shown in Figures 6 and 7.

Safety
No deaths occurred during the study, and no patient withdrew because of an AE. One serious AE was reported...
Figure 6. (A, C, E) This 55-year-old woman is shown on postoperative day 1, after rhytidectomy. The left side of her face received standard-of-care treatment plus fibrin sealant, and the right side of her face received standard-of-care treatment only. (B, D, F) Postoperative day 7.
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Of the 7 hematomas that occurred (all on the SoC-only side) during the study, 6 were mild in severity according to the reporting investigator and 1 was moderate. All patients recovered completely from this event. As noted above, no hematomas occurred on the side of the face treated with fibrin sealant.

Other nonserious facial AE were experienced by 4 patients (9%) exclusively on the side treated with SoC alone: edema (n = 1), seroma (n = 2), and epidermolysis (n = 1). One patient (2%) had a facial AE (wound dehiscence, classified as mild and unrelated to treatment) exclusively on the side treated with FS VH S/D 4 s-apr. Three patients (7%) experienced a facial AE on both sides of the face (edema in all 3 cases).

**DISCUSSION**

Although postoperative ecchymosis is an expected physiologic outcome of surgery, it remains a major concern in many surgical disciplines, particularly aesthetic and reconstructive surgery. Various studies have suggested that the use of fibrin sealants may reduce the degree of ecchymosis in patients who undergo rhytidectomy; however, such an improvement was not observed in the present study. It is possible that the physical trauma associated with early removal of drains (24 hours postoperatively) contributed to higher levels of ecchymosis, particularly on the sides of the face treated with fibrin sealant. Although FS VH S/D 4 s-apr should promote healing and tissue adherence, removing drains from areas where it has been used may be more complicated than with SoC, thus increasing the likelihood and degree of ecchymosis. Another study demonstrated that the presence and negative pressure of drains can disrupt the action of fibrin sealant.

In the present study, although bruising assessments at early time points generally favored SoC-only treatment, by day 7 the level of bruising was similar for both treatments.

On day 3, patient-reported treatment preferences strongly favored FS VH S/D 4 s-apr. Although this finding is inconsistent with the blinded reviewers’ visual assessments on day 3, it may be explained by the fact that patient preferences were influenced by factors other than bruising.

Findings from this study question the utility of a blinded review panel and a modified Marchac grading system for assessing postoperative ecchymosis in the setting of a multicenter study. Even though the photographic equipment was identical at all sites, and the equipment and lighting were set up by the same medical imaging...
Figure 7. (A, C, E) This 46-year-old woman is shown on postoperative day 1, after rhytidectomy. The left side of her face received standard-of-care treatment only, and the right side of her face received standard-of-care treatment plus fibrin sealant. (B, D, F) Postoperative day 7.
company, there were inconsistencies among the reviewers’ grading of ecchymosis, as well as inconsistencies between individual reviewers’ gradings (intraobserver) and visual-comparison outcomes for the same patient. Kappa coefficients indicated only slight interobserver agreement among the blinded reviewers.

The most objective and measurable outcome in the present study was drainage volume at 24 hours. Drainage volumes from the sides of the face treated with FS VH S/D 4 s-apr were significantly lower than from the sides treated with SoC alone. Moreover, the fact that no hematoma or seroma occurred on any of the sides treated with FS VH S/D 4 s-apr suggests that drainage reduction can be achieved without increasing the risk of hematoma or seroma. Further testing of this observation was performed in our companion phase 3 clinical trial of FS VH S/D 4 s-apr in patients undergoing rhytidectomy. Results of the phase 3 study also demonstrated that treatment with FS VH S/D 4 s-apr resulted in significantly lower drainage volumes than treatment with SoC alone. Furthermore, the use of FS VH S/D 4 s-apr reduced the mean drainage volume from levels that would require drain placement to a level well below the threshold for drain justification. Other studies have shown that fibrin sealants have similar effects on drainage.

The use of aerosolized fibrin sealants in patients who undergo rhytidectomy has been associated with lower rates of ecchymosis compared with SoC alone. In a study of 200 patients, prolonged ecchymosis and edema were observed in 12% of patients who received SoC alone and in just 2% of those who received adjuvant Tissucol (Baxter Healthcare Corp [Immuno AG, Vienna Austria]) (P < .006). Similarly, in a study of 48 patients by Fezza et al, those who received aerosolized fibrin glue had significantly less edema and ecchymosis than those who did not receive it (P < .0001). In both of these studies, patients were randomized to receive either aerosolized fibrin sealant (without drains) or SoC alone (with drains) on both sides of the face. However, in our study, drains also were used with FS VH S/D 4 s-apr treatment, which may have affected the incidence and severity of ecchymosis and edema.

Hematoma can be a major complication after rhytidectomy. According to retrospective analyses, the incidence ranges from 0.2% to 8%. The relatively high incidence of hematoma in the present study (7 of 45 patients; 16%) may be attributed to the fact that patients were monitored closely during the study because hematoma was a specific outcomes end point. All but 1 of the hematomas in the present study were mild in nature (the other was moderate); none required surgical intervention, and all resolved completely. All 7 hematomas were on the SoC-only sides of the face, suggesting that they were not a result of drain usage. Drains were used on both sides of the face, so if

Figure 7. (continued) (A, C, E) This 46-year-old woman is shown on postoperative day 1, after rhytidectomy. The left side of her face received standard-of-care treatment only, and the right side of her face received standard-of-care treatment plus fibrin sealant. (B, D, F) Postoperative day 7.
hematomas were caused by drain usage, we would have expected to see them on both sides of the face.

The occurrence of seroma is relatively uncommon in rhytidectomy,\(^{19}\) and drain use during the first 24 hours after surgery has been associated with a lower risk of seroma.\(^{2}\) Only 2 cases of seroma occurred in our study, both on the sides of the face that received SoC only.

Treatment with FS VH S/D 4 s-apr was associated with a good safety profile in our study. This finding is consistent with other clinical trials of Baxter’s fibrin sealant, FS VH S/D 4 s-apr, including a study in burn patients\(^{11}\) and the phase 3 companion to the present study.\(^{16}\)

**CONCLUSIONS**

Results of this exploratory study show that the use of FS VH S/D 4 s-apr in rhytidectomy appears to be safe. The study also demonstrates that drainage volume, an objective end point for evaluating efficacy, is significantly lower when FS VH S/D 4 s-apr is added to SoC treatment. Statistically significant differences in ecchymosis and edema, as assessed visually from postoperative photographs, were not demonstrated between the study groups in this multicenter trial that included drain use in all patients.

**Disclosures**

Drs Nguyen, Gerut, Chen, Diamond, Shire, and Hester are paid consultants for Baxter Healthcare Corporation, the manufacturer of products discussed in this study. Ms Silvati-Fidell and Drs Desmond and Abrams are employed by Baxter and hold stock and share options in the company.

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