



Preliminary Report

Facelift Patients Receiving Intraoperative Administration of a Self-assembling Hemostat Agent Experienced Minimal Bruising and No Acute Hematomas: A Pilot Study

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Abstract

Background: Hematomas are consistently cited as the most common complication of facelift surgery, with reported incidence rates ranging from 1% to 9% despite preventative measures. A self-assembling RADA16 peptide solution (PuraSinus, 3-D Matrix, Newton, MA) designed to aid in wound healing, adhesion prevention, and bleeding control has demonstrated hemostatic control of intra- and postoperative bleeding associated with various surgical procedures, including nasal and sinus surgery.

Objectives: To report surgical experience using novel application of RADA16 hemostatic agent in facelift procedures.

Methods: Through exploring incorporation of RADA16 hemostatic agent into standard of care, 15 higher-risk facelift patients were treated intraoperatively between December 2020 and July 2021. Postoperative follow-up was on post-procedure day 1 and 3 and at approximately one week. During follow-up, potential complications were assessed subjectively, including hematoma, swelling, and bruising; postoperative observations recorded; and photographs taken.

Results: Among facelift patients receiving intraoperative RADA16 hemostatic agent there were no hematomas or protracted ecchymosis events. The only significant complication was one patient admitted for intravenous hydration due to post-operative nausea and vomiting. All patients had minimal bruising or a dramatic absence of bruising and experienced no hemorrhage or hematoma. Through surgical experience, technique for RADA16 hemostatic agent placement was optimized and procedural details are provided.

Conclusions: Intraoperative administration of topical RADA16 hemostatic agent appears to deter acute hematoma and hemorrhage formation and early experience suggests that RADA16 hemostatic agent may also attenuate post-operative bruising in facelift patients. These observations warrant further investigation in a larger randomized controlled study.

Level of Evidence: 4

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During a rhytidectomy, facial rejuvenation is accomplished through dissection of subcutaneous layers and pulling of the skin to create a more youthful appearance.¹ As one of the most common aesthetic procedures in the United

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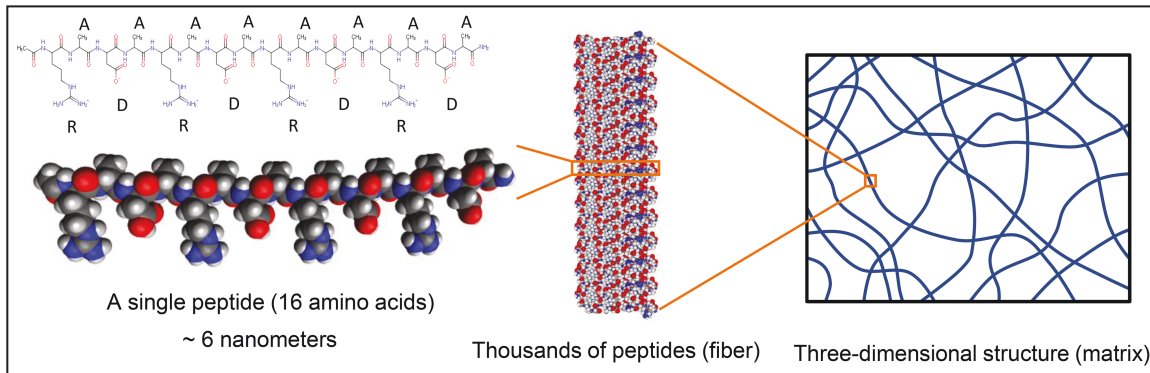


Figure 1. RADA16 (PuraSinus, 3-D Matrix, Newton, MA) is a 16-amino acid self-assembling peptide containing repeated sequences of 3 amino acid residues: positively charged arginine (R), hydrophobic alanine (A), and negatively charged aspartic acid (D). In an acidic environment (pH \approx 2), hydrophobic residues and positively charged sequences along the RADA16 peptide arrange the monomers into stable β -sheet nanofibers with a positively charged surface to create a very viscous solution that flows easily.

States, facelift ranked in the top 5 cosmetic surgical procedures performed by The American Society of Plastic Surgery members, with 234,374 procedures completed in 2020.² Furthermore, facelift represented the most frequent surgical procedure performed for patients above the age of 70 years.³ Despite the introduction of numerous nonsurgical procedures to address facial aging, surgical facelift remains the standard for correcting descent of facial features and tissue laxity characteristic of the aging face.⁴

Although facelift is considered a very safe procedure when performed by a board-certified plastic surgeon, as with any surgery, it is accompanied by a risk of complications.⁵ Patient dissatisfaction with the cosmetic result can occur due to scarring, contour irregularities, hyperpigmentation, or alopecia.⁶ Complications, such as hematoma formation, infection, nerve damage, bruising, skin slough or necrosis, facial telangiectasia, edema, seroma, and wound healing can occur, as can systemic complications such as deep vein thrombosis (DVT), pulmonary embolism (PE), stroke; and anesthetic complications.^{1,5,7-11}

Hematomas occur when blood pools beneath the skin, outside the blood vessels, and can be classified as major or minor in severity. Both types are of significant concern, as each negatively affects patient outcomes. Hematomas are consistently cited as the most common complication of facelift surgery, with reported incidence rates ranging from 1% to 9%.^{4,5,7,8,11,12} Given the significance of the event, prevention of hematoma formation is a high priority, especially given that while serious complications do occur, most often, for patients, the most troubling complications are those that lengthen social downtime. Bruising in particular can take a substantial amount of time to dissipate and is often the chief complaint of patients who do not feel they are ready for social activity within 2 weeks. Risk factors

for postoperative hemorrhage and hematoma formation include age, gender, hypertension, anticoagulant use, surgical techniques, and postoperative management, and a relatively large proportion of facelift patients in clinical practice can be classified as high risk.^{6,13} For patients with elevated risk, the rate is likely far higher, and there remains an unmet need for effective prevention and/or interventions that reduce the risk further.⁵

On an independent investigational basis starting in December 2020, the senior author began using PuraSinus (3-D Matrix, Newton, MA) intraoperatively for facelift and other aesthetic surgical procedures in patients who were at high risk for hematoma formation. PuraSinus is a 2.5% synthetic aqueous RADA16 peptide solution cleared for use in the United States as an intraoperatively applied hemostatic wound dressing that prevents adhesion formation and assists wound healing after nasal surgery or trauma.¹⁴

RADA16 is a synthetic 16-amino acid peptide that self-assembles to form β -sheet nanofibers in acidic aqueous solutions (Figure 1).¹⁵ The self-assembled RADA16 nanofibers spontaneously cross-link to become a complex mesh-like hydrogel structure resembling the native extracellular matrix architecture (Figure 1).¹⁵⁻²⁰ This self-assembly is spontaneous and reversible upon exposure to an external shearing force, allowing for enhanced flowability during delivery, followed by an immediate return to the viscous state. Thus, in clinical practice, the shear-thinning and thixotropic properties allow RADA16 administration through a narrow applicator to flow easily to the wound or surgical site before the spontaneous formation of a hydrogel upon contact with blood or other physiological fluids, effectively blocking blood flow (Figure 2).¹⁵

During facelift procedures, RADA16 has the potential for eliminating dead space, serving as a scaffold for expedited healing, and preventing postoperative bruising

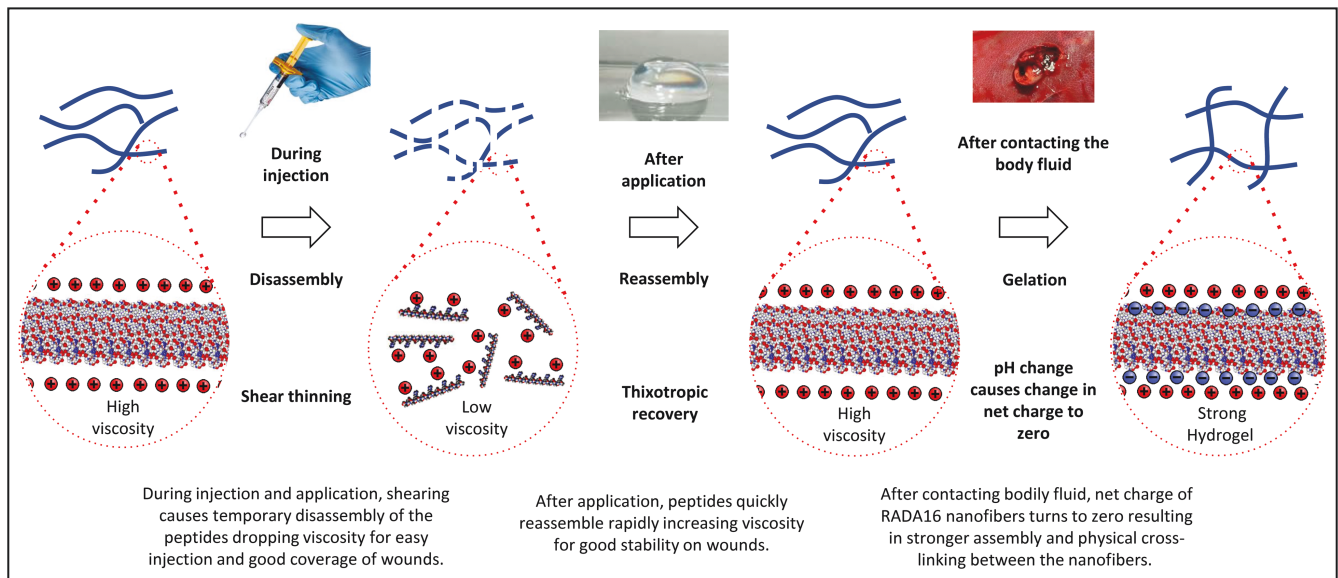


Figure 2. Self-assembly is spontaneous and reversible upon exposure to an external shearing force, followed by an immediate return to the viscous state. Upon contacting the physiological pH, the peptide solution is neutralized and buffered through the deprotonation of aspartic acid residues, which become negatively charged and create a net peptide charge of zero. As a result, nanofiber surfaces become hydrophobic and physically cross-link through hydrophobic interactions to become a complex mesh-like hydrogel structure resembling native extracellular matrix (ECM) architecture.

and hematoma formation. Over the course of 15 facelift procedures, the surgical technique was optimized and is presented here. Furthermore, the dramatic reduction of bruising in the patients reported here has prompted the adoption of RADA16 as a standard of care in the author's practice for all facelift procedures.

METHODS

Study Design

This study is a retrospective review of 15 patients treated with placement of RADA16 hemostatic agent on all tissue surfaces before skin closure following facelift between December 2020 and July 2021 (Video 1). Patients were nonconsecutive and self-selected based on risk and expense: patients were educated on their personal risk factors for bruising and hematoma and were offered RADA16 at an additional cost as a preventative agent. This report includes the first 15 patients who elected to use the agent. While the RADA16 hemostatic agent is used in other surgical applications, including nasal surgery, its application in facelift surgery is novel. In this pilot study, the patients are classified as high risk based on one or more of the following risk factors: age above 45 years, male, previous history of surgical bleeding despite negative hematological evaluation, thin tissues, self-reported easy bruising, or intraoperative evidence of a capillary leak. All patients



Video 1. Watch now at <http://academic.oup.com/asjopenforum/article-lookup/doi/10.1093/asjof/ojac037>

were medically cleared by their primary care physician before surgery and were classified as American Society of Anesthesiologists physical status classification system status of 1 or 2. All patients received monitored anesthesia by a certified anesthetist. Postoperative follow-up occurred on postprocedure day 1 (in person) and day 3 (telemedicine) and then approximately 1 week later (in person). During each follow-up, the following potential complications were assessed subjectively: swelling, hematoma, bruising, discoloration, scarring, raised skin, skin folds, loose skin, and little bumps/granuloma. Postoperative photographs were taken when possible. This study is an investigational, investigator-initiated retrospective review

and thus did not obtain IRB approval. All treatments adhered to the Good Clinical Practice and standards set forth in the World Medical Association's Declaration of Helsinki. Consent for treatment and all included photographs and video was obtained.

Surgical Technique

Patients were marked in the holding area before surgery. After the patients were prepped and draped under sterile conditions and monitored anesthesia, 1% lidocaine with epinephrine (1:100,000) was injected into all planned incisions. Wetting local anesthesia, 30 mL of normal saline with 1% lidocaine and epinephrine (1:100,000), was then injected along areas of planned skin flap undermining. Retaining ligaments were released to mobilize the superficial musculoaponeurotic system (SMAS). For the jawline and neck, a deeper plane was developed to ensure lateral platysma and SMAS movement. Either SMASectomy¹⁴ or SMAS plication²¹ was used in combination with spanning suture fixation of the lateral platysma to the mastoid fascia in a deep permanent suture, superficial absorbable double-layer inset. A tailor tacking skin inset was done to minimize undue tension on skin flaps. Before complete closure of the skin flaps, meticulous hemostasis was double-checked by cautery. Next, one 3 mL syringe per side of RADA16 was placed topically: the gel is placed close to the incision and then spread uniformly through the dissected subcutaneous planes as a thin film. Following partial closure of the skin flap, application of light external pressure on the skin was used to express any excess gel, followed by complete closure. This removal of excess gel prevents fluid accumulation and any possible resulting contour irregularities. The complete procedure is shown in [Video 1](#). While the neck was opened in 11 of the 15 patients (73.3%), RADA16 was only placed around the ears. There were no drains placed. For compression, patients were instructed to wear a chin strap for 12 hours a day for 1 week, but otherwise, no additional preventative measures were taken.

RESULTS

Patient Characteristics

From December 2020 to September 2021, 15 patients with a mean age of 59.3 years (range 48-75 years) received a facelift with intraoperative, topical RADA16 administration. Patients received a facelift either alone or combined with various surgical and nonsurgical facial aesthetic procedures, such as blepharoplasty, liposuction, and fat injection ([Table 1](#)). Most (n = 14, 93%) patients were females and 1 (7%) was male.

Table 1. Baseline Demographic Characteristics of Patients

Treatment cohort features	
Demographic characteristic	(N = 15)
Age, years	
Mean (range)	59.3 (48-75)
Sex (male/female, n [%])	
Male	1 (7)
Female	14 (93)
Procedure type, n (%)	
Facelift alone	3 (20)
Forehead lift	1 (7)
Bilateral blepharoplasty	8 (53)
Fat injection	5 (33)
Liposuction	4 (27)
Browpepy	1 (7)
Halo laser	2 (13)
Absorbable suspension Sutures	1 (7)
Deoxycholic acid	1 (7)
Fitzpatrick skin type (I-VI)	
I	9 (60)
II	3 (20)
III	2 (13)
IV	—
V	1 (7)
VI	—

Outcomes

Complications were very minimal, and no acute hemorrhage or acute hematoma was reported. Intraoperative administration of the RADA16 hemostatic agent appears to deter the formation of hemorrhage and hematoma. Patients in the pilot study experienced no postoperative issues related to RADA16, except for the small (less than 3 mL) accumulation of serosanguinous fluid in 3 patients in the neck, which were promptly percutaneously drained and resolved with one aspiration. The fluid accumulation seemed related to both excess hydrogel placement and noncompliance with postoperative activity. With this hypothesis in mind, the senior author modified his technique to include the 3 mL volume per side, but with application of light external light pressure on the skin after partial closure to allow the excess gel to exit along a small opening in the suture line, which eliminated the accumulation of serosanguinous fluid in subsequent patients. A total of 3 patients had postoperative hypertension, which was corrected by medications. The single significant complication was a 23-hour hospital admission of a patient with a history of postoperative nausea and vomiting for intractable nausea developed after surgery for intravenous hydration and observation. Remarkably, despite repeated emesis, the patient had negligible ecchymosis, failed to develop a hematoma, and went on to have an uneventful postoperative course.



Figure 3. A 48-year-old female patient at (A) baseline, (B) postoperative day 1, and (C) postoperative day 3. The patient experienced essentially no bruising following a lower facelift with RADA16 (PuraSinus, 3-D Matrix, Newton, MA) administration.



Figure 4. A 63-year-old female patient experienced minimal bruising following a full facelift with RADA16 (PuraSinus, 3-D Matrix, Newton, MA) administration. Photographs shown (A) before surgery and (B) on postoperative day 1.

Of note, all patients had minimal bruising or a dramatic absence of bruising, suggesting that intraoperative topical treatment with RADA16 helps control postoperative bruising. Most notable was the surprising lack of bruising in the patient shown in [Figure 3](#), following a facelift on postoperative day 1, an absence that is even more pronounced on postoperative day 3. This pattern of almost no bruising occurred in one other additional patient, who noted that she had almost no bruising on day 3 following a mini facelift with RADA16 treatment. Images from the patient shown in [Figure 4](#) following facelift on postoperative day 1 show the minimal extent of bruising typical of most patients in this study. Overall, these patients experienced excellent

results with no hemorrhage or hematoma and minimal bruising, as evident in the after photographs of 2 patients more than 30 days out from full facelift surgery ([Figure 5](#)). While more formal study is needed to fully characterize this outcome, and to confirm this benefit of treatment, the reported duration of bruising was far shorter than for patients who had bruising without RADA16.

DISCUSSION

In this observational pilot study of 15 patients, intraoperative topical administration of the hemostatic agent RADA16 appears to deter acute hemorrhage and acute hematoma



Figure 5. Patients receiving facelift surgery with RADA16 (PuraSinus, 3-D Matrix, Newton, MA) administration experienced minimal complications and excellent results. A 76-year-old female patient (A) before and (B) 40 days after a full facelift, forehead lift, upper and lower blepharoplasty, fat injection, and neck liposuction; a 63-year old female patient (C) before and (D) 89 days after a full facelift, bilateral lower blepharoplasty, and fat injection.

formation and minimize postoperative bruising in facelift patients. In fact, RADA16's apparent benefits and ease of use in facelift surgery have led the senior author to integrate it as the standard of care for his practice, even for non-high-risk patients, as hematomas also occur in non-high-risk patients. The hypothesis that RADA16 is responsible for lessening the outcomes of postoperative bleeding in this study is consistent with studies of similar products, demonstrating hemostasis in cardiovascular, digestive endoscopic, and endonasal surgery.²²⁻²⁴ While these benefits are based on clinical observation only, and the sample size of this pilot study is too small to draw formal conclusions, the outcome is striking and warrants more formal

study in a controlled clinical trial. In this study, the higher-risk patients were those who felt that the expense of the product was justified, but ultimately, the data presented suggest a broader benefit to all patients undergoing a facelift, as hematomas occur in normal-risk patients as well.

Bruising is an expected outcome following facelift surgery; however, it is unfavorable to patients as it potentially leads to embarrassment around having had the procedure done, unsolicited questions, or even assumed spousal abuse, all of which amounts to social downtime.²⁵ Improving and expediting postoperative healing is a common priority for both patients and physicians.²⁶ In this study, RADA16 treatment appeared to minimize and,

In some cases, eliminate postoperative bruising in patients receiving facelift surgery, supporting a more rapid return to social life. In those patients who did experience bruising, severity was minor when compared with what one might expect given individual patient risk factors, and the duration of bruising was lessened substantially. The potential for RADA16 to improve bruising is an attractive benefit of this product, especially considering how quickly and easily it can be administered intraoperatively.

Hematoma formation following facelift surgery is highly undesirable as it may require operative intervention and can contribute to a difficult postoperative recovery with prolonged edema, subsequent fibrosis, and irregularities in the subcutaneous plane that can compromise the final outcome.^{7,27} Furthermore, expanding hematomas can lead to flap ischemia and tissue loss resulting in disfiguring scars as well as life-threatening airway compromise.²⁷ Male gender has been identified as a risk factor for developing major hematoma following facelift surgery, possibly due to generally thicker and more vascular skin.^{5,28} Additional factors associated with hematoma risk include hypertension, coagulopathy or use of anticoagulants, and postanesthesia nausea, vomiting, and pain.⁶ Ambiguity lies in whether the type of facelift performed can influence the incidence of hematoma, which was investigated in 2 recent meta-analyses.^{7,29} Although one study showed no statistically significant difference in hematoma incidence among SMAS flap, SMAS plication, and deep-plane techniques,⁷ the second demonstrated an increased risk of major hematoma for deep plane vs SMAS plication and SMASectomy vs SMAS plication.²⁹

Major bleeding tends to present within 24 hours of surgery with symptoms of subcutaneous mass, pain, and ecchymosis and requires surgical intervention to stop the hemorrhage.⁶ Such hematomas can endanger the vascularity of the skin flaps and delay postoperative recovery.³⁰ In contrast, minor bleeding is often delayed and is managed non-surgically by drainage or aspiration.^{6,29,30} Perhaps the most objective measure of the major complications associated with facelift surgery can be extracted from a large prospective study conducted on a cohort of patients enrolled in the CosmetAssure (Birmingham, AL) insurance program, which covers unexpected major complications from cosmetic surgical procedures.⁵ The primary outcome was the occurrence of a major complication within 30 days of surgery that required hospital admission, emergency room visit, or a reoperation. It excluded any complications manageable in the clinic. Among 11,300 patients receiving facelifts, the overall complication rate was 1.8%. Of these complications, 62% were hematomas, representing an overall incidence rate of 1.1%. This number is significantly understated as nonoperative, local management of blood accumulation is rarely reported as a complication due to the lack of hospitalization or need for formal reoperation.

Perioperative procedures have been adopted to reduce postoperative hematoma in facelift patients. Precautions include preoperative discontinuation of antiplatelet medications or anticoagulants known to increase bleeding as well as the postoperative control of blood pressure, nausea, and pain.^{6,12} Intraoperatively, surgeons can decrease the risk of hematoma by achieving meticulous hemostasis before closure.⁶ Drain placement is common during facelift surgery and can reduce ecchymosis. Additionally, tranexamic acid (TXA) has been shown to lessen intraoperative bleeding, and fibrin sealants decrease ecchymosis, drainage, and swelling.^{6,31} For TXA, systemic use (1 g IV) is commonly used to prevent bleeding in cardiac, orthopedic, dental, trauma, and critical care, especially for patients with bleeding disorders or on antithrombotic medications. More recently, TXA has been reported in facelift surgery as part of an infiltration procedure.³² The benefit of these measures for reducing hematomas as well as how they would affect bruising in comparison to the application of RADA16 remains unclear.³¹ It is also important to note that TXA has contraindications, with absolute contraindications including, but not limited to, a history or family history of PE, DVT, or thrombotic cardiac rhythm disease and color blindness (an indicator of toxicity). Relative contraindications include oral contraceptives and renal impairment.³³ For more mature patients, in particular, TXA may not be the safest option for reducing risk of hematoma, and the potential for serious complications highlights the unmet clinical need. While the above-listed measures have resulted in some reduction in the incidence of hematoma, it remains the most common complication of facelift surgery.⁵

An ideal hematoma prevention agent would be easy to administer, non-systemic, rapid-acting, effective, biocompatible, non-animal derived, resorbable, easy to use, and cost-effective.¹⁵ While there are no such treatments directly marketed for facelift procedures, RADA16 satisfies all of these requirements. RADA16 has been adopted by surgeons for various clinical applications. It is cleared by the US FDA for use in nasal surgery for trauma or repair³⁴ (PuraSinus) as well as CE marked for use in Europe (PuraStat, PuraBond) (3-D Matrix Europe SAS, Caluire-et-Cuire, France) for hemostasis during surgical procedures. To our knowledge, RADA16 has not been formally described for use in aesthetic surgery, and this pilot study represents the first time that it has been used in facelift surgery.

Importantly, the RADA16 hemostatic agent is easy to administer and does not disrupt workflow. Recently, placement of an extensive system of quilting sutures known as a "hemostatic net" following facelift was shown in a 2013 study of over 500 patients to eliminate early hematomas.³⁵ However, in almost a decade since its introduction, the use of the hemostatic net has not become generally accepted, perhaps in part due to interruption

of workflow or the time-consuming nature of the procedure.^{27,31} This speaks to the centrality of usability and efficiency in this area. In contrast, the intraoperative use of RADA16 hemostatic as a topical agent may offer the benefit of eliminating or reducing acute hematoma in facelift surgery through a less intimidating, easy-to-administer, unobtrusive technique.

Although this study shows promise for the integration of RADA16 administration in facelift surgery, this pilot study was observational in nature. Other study limitations are its small size, lack of controls, and lack of objective, quantifiable outcomes. The utility of the RADA16 hemostatic agent in facelift surgery should be studied more broadly, ideally in a randomized controlled study. Considering that males are at higher risk for developing hematomas, enrolling more male patients is critical to further understand its efficacy as a hematoma prevention agent in facelift surgery.

CONCLUSIONS

Observation of the postoperative effects of administration during facelift surgery in this pilot study suggests that the RADA16 hemostatic agent prevents acute hematoma/hemorrhage formation and minimizes postoperative bruising in facelift patients. A randomized controlled study, enrolling a substantial number of male patients, is needed to further assess the efficacy of intraoperative topical administration of RADA16 hemostatic agent in facelift surgery.

Supplemental Material

This article contains supplemental material located online at www.asjopenforum.com.

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Disclosures

Dr Few is a consultant and investigator for Merz (Raleigh, NC) and Allergan (Irvine, CA); is a consultant for Revance (Nashville, TN); holds stock in Venus Concept (Toronto, Canada) and Revance; and is part owner of Aforé, LLC (Chicago, IL).

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