



EFFICACY OF RADA-16 SELF-ASSEMBLING PEPTIDE HYDROGEL IN THE MANAGEMENT OF EPISTAXIS: A SYSTEMATIC REVIEW

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ABSTRAK

Epistaksis merupakan kondisi yang umum dijumpai dalam bidang otolaringologi dengan beban klinis yang signifikan, terutama pada kondisi pascaoperasi dan pasien dengan *hereditary hemorrhagic telangiectasia* (HHT). Hidrogel peptida *self-assembling* RADA-16 telah muncul sebagai agen hemostatik baru. Tinjauan sistematis ini bertujuan mengevaluasi efektivitas dan keamanan RADA-16 dalam penatalaksanaan epistaksis. Tinjauan dilakukan sesuai pedoman PRISMA 2020 melalui penelusuran literatur pada PubMed, Cochrane Library, dan Google Scholar. Studi uji terkontrol secara acak dan studi observasional yang mengevaluasi penggunaan RADA-16 untuk epistaksis disertakan. Luaran meliputi keberhasilan hemostasis, perdarahan ulang, kebutuhan intervensi tambahan, kenyamanan pasien, dan komplikasi. Risiko bias dievaluasi menggunakan *Joanna Briggs Institute* dan data disintesis secara naratif. Lima studi dengan 1.298 pasien disertakan, terdiri atas satu uji terkontrol secara acak, dua studi kohort, dan dua seri kasus, dengan sebagian besar bukti berasal dari studi observasional. RADA-16 menunjukkan efektivitas hemostatik yang tinggi pada berbagai kondisi klinis. Studi kohort ($n = 985$) melaporkan perdarahan pascaoperasi yang lebih rendah dibandingkan perawatan standar (0,35% vs. 2,17%), sedangkan seri kasus multisenter ($n = 167$) melaporkan keberhasilan hemostasis 98,2% dan adhesi 4,2%. Pada pasien HHT ($n = 22$), *Epistaxis Severity Score* menurun 2,0 poin. Tidak dilaporkan kejadian tidak diinginkan yang serius. RADA-16 berpotensi sebagai agen hemostatik yang aman dan efektif, tetapi bukti masih terbatas oleh heterogenitas studi dan dominasi desain observasional. Uji klinis acak berkualitas tinggi diperlukan untuk memperkuat bukti efektivitas dan keamanannya.

Kata Kunci: *Epistaksis, RADA-16, Peptida Self-Assembling*

ABSTRACT

Epistaxis is a common condition in otolaryngology with a significant clinical burden, particularly in postoperative settings and patients with hereditary hemorrhagic telangiectasia (HHT). The self-assembling peptide hydrogel RADA-16 has emerged as a novel hemostatic agent. This systematic review aimed to evaluate the effectiveness and safety of RADA-16 in epistaxis management. The review followed the PRISMA 2020 guidelines, with literature searches conducted in PubMed, the Cochrane Library, and Google Scholar. Randomized controlled trials and observational studies evaluating RADA-16 for epistaxis were included. Outcomes included hemostatic success, rebleeding, additional interventions, patient comfort, and complications. Risk of bias was assessed using the Joanna Briggs Institute tools, and data were synthesized narratively. Five studies involving 1,298 patients were included: one randomized controlled trial, two cohort studies, and two case series, with most evidence derived

from observational studies. RADA-16 demonstrated high hemostatic effectiveness across clinical settings. A large cohort study ($n = 985$) reported lower postoperative bleeding compared with standard care (0.35% vs. 2.17%), while a multicenter case series ($n = 167$) reported 98.2% hemostatic success and 4.2% adhesion. In patients with HHT ($n = 22$), the Epistaxis Severity Score decreased by 2.0 points. No serious adverse events were reported. Overall, RADA-16 shows potential as a safe and effective hemostatic agent, although evidence remains limited by study heterogeneity and the predominance of observational designs. High-quality randomized trials are needed to confirm its effectiveness and safety.

Keywords: *Epistaxis, RADA-16, Self-Assembling Peptide*

INTRODUCTION

Epistaxis, or nosebleed, represents one of the most prevalent otolaryngologic complaints encountered in clinical practice, affecting individuals across a broad spectrum of etiologies from idiopathic spontaneous bleeding to disease-related and postoperative hemorrhage. Among the most challenging presentations is epistaxis associated with hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant vascular disorder affecting up to 1 in 5,000 individuals worldwide, in which recurrent and often severe nasal bleeding occurs in over 90% of patients and significantly diminishes quality of life (Adelman et al., 2025). HHT is characterized by abnormal development of blood vessels, including mucosal telangiectasia that commonly manifests as recurrent epistaxis and may require long-term multidisciplinary management (Hammill et al., 2021; Hermann et al., 2025). Similarly, epistaxis constitutes a major postoperative complication following endonasal surgical procedures including functional endoscopic sinus surgery (FESS), turbinate reduction, and septoplasty with reported bleeding incidences ranging from 2% to 15% depending on the procedure and patient population. Given these clinical burdens, the identification of safe, effective, and easily applicable hemostatic agents remains a priority in rhinologic practice. (Soodin et al., 2022; Xu et al., 2025; Faughnan et al., 2020)

Management postoperative and disease-related epistaxis has involved a mix of cauterization, nasal packing, and topical agents. However, standard methods like non-absorbable packing and diathermy are often limited by patient discomfort, the risk of tissue damage, and the frequent need for surgical intervention. Alternative medical approaches have also been investigated, including tranexamic acid, with evidence suggesting potential benefits for reducing the severity or recurrence of epistaxis in selected patient populations (Kamhieh & Fox, 2016). For epistaxis associated with HHT, laser-assisted treatment has likewise been evaluated as an approach to controlling recurrent bleeding, although treatment outcomes and durability vary across available studies (Abiri et al., 2020). While bioresorbable materials have offered some improvement, no single agent has yet become the definitive gold standard. This has led to increased interest in RADA-16 (commercially known as PuraStat® or PuraGel®), a synthetic self-assembling peptide hydrogel. Once it meets physiological fluids, it spontaneously forms a transparent nanofiber scaffold that acts as a physical barrier, effectively stopping bleeding regardless of the patient's own coagulation status (Soodin et al., 2022; Xu et al., 2025; Janapala et al., 2022; Reuben et al., 2021).

Despite an expanding body of evidence supporting RADA-16's utility across multiple surgical specialties including gastrointestinal endoscopy and cardiovascular surgery its application within rhinology and epistaxis management remains relatively nascent. Existing studies are largely limited to small retrospective cohorts and case series, and the evidence base

specifically pertaining to epistaxis whether postoperative, traumatic, or disease-related has yet to be systematically appraised. For instance, while Adelman et al. (2025) demonstrated a clinically significant reduction in Epistaxis Severity Scores among HHT patients, and Xu et al. (2025) reported a markedly lower postoperative bleeding rate following inferior turbinate submucosal resection, these studies remain methodologically heterogeneous and insufficiently synthesized (Adelman et al., 2025; Xu et al., 2025). Furthermore, the only randomized controlled trial to date focused primarily on pain reduction during postoperative debridement rather than hemostatic efficacy as a primary endpoint, underscoring the need for more rigorous and comprehensive evidence synthesis (Hur et al., 2024; Gelain et al., 2021; Lee et al., 2019).

Thus, although individual studies have reported favorable outcomes, there is currently no comprehensive systematic synthesis specifically evaluating the hemostatic effectiveness and safety of RADA-16 across different clinical presentations of epistaxis. The limited number of randomized trials, predominance of observational evidence, and heterogeneity in clinical settings and outcome measures further limit the strength of current conclusions. This evidence gap provides a clear rationale for conducting a systematic review to integrate the available findings and clarify the clinical utility, safety profile, and consistency of RADA-16 in epistaxis management.

This systematic review seeks to systematically evaluate the current evidence on RADA-16, a self-assembling peptide hydrogel, to determine its effectiveness and safety in the management of epistaxis. The analysis looks across several clinical landscapes, specifically focusing on postoperative nasal bleeding and disease-driven episodes like those seen in HHT. By synthesizing evidence from different study designs and clinical settings, this review aims to clarify the magnitude and consistency of the reported hemostatic benefits, as well as potential safety concerns. Where comparative data are available, RADA-16's performance is also examined against established hemostatic approaches to provide a clinically relevant assessment of its potential role in contemporary epistaxis management.

The scope of the review is broad, incorporating a mix of randomized controlled trials, prospective and retrospective cohorts, and case series. To be included, these studies must have examined the use of RADA-16 within nasal or endonasal environments, using epistaxis-related outcomes as a primary or secondary measure. This approach is intended to address the current evidence gap by bringing together the available evidence on hemostatic success, rebleeding, additional interventions, patient comfort, and complications across diverse clinical contexts.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A structured literature search was performed across PubMed, Cochrane Library, and Google Scholar to identify relevant studies evaluating the use of RADA-16 in the management of epistaxis.

Eligibility Criteria

Studies were selected based on predefined PICOSTD criteria. Eligible studies included patients presenting with epistaxis (anterior or posterior; spontaneous or iatrogenic). The intervention of interest was topical application of RADA-16 self-assembling peptide hydrogel, compared with conventional management strategies such as nasal packing, cauterization, or alternative hemostatic agents. Outcomes of interest included hemostasis success, time to bleeding control, rebleeding rates, requirement for additional interventions, patient comfort,

and treatment-related complications. Only randomized controlled trials and observational studies (including cohort studies, case-control studies, and case series with at least five patients) were included. Studies were required to report a minimum follow-up duration of 24 hours.

Search Strategy

A comprehensive literature search was conducted using a combination of Medical Subject Headings (MeSH) and free-text terms related to epistaxis and RADA-16. The search was conducted for studies published between 2020 and 2025, with the final search performed in 2025. The search was performed in PubMed, Cochrane Library, and Google Scholar using keywords and their variations, including “epistaxis,” “nasal bleeding,” “RADA-16,” “self-assembling peptide,” “RADA16,” and related commercial names such as “PuraStat” and “PuraGel.” Reference lists of the included studies were also manually screened to identify additional relevant articles.

Study Selection and Data Extraction

All identified records were screened in a two-stage process. Initially, titles and abstracts were reviewed to exclude irrelevant studies. Full-text articles were subsequently assessed against the eligibility criteria. Data extraction was performed using a standardized form, capturing study characteristics, patient demographics, intervention details, comparator information, and reported outcomes.

Risk of Bias Assessment

The methodological quality of included studies was evaluated using the Joanna Briggs Institute (JBI) critical appraisal checklists appropriate to each study design. Domains assessed included selection bias, measurement validity, confounding factors, and appropriateness of statistical analyses. Each study was categorized as having low, moderate, or high risk of bias.

Data Synthesis and Statistical Analysis

Due to heterogeneity in study design, patient populations, and outcome measures, a quantitative meta-analysis was not feasible. Therefore, findings were synthesized using a narrative approach, focusing on key clinical outcomes such as hemostatic effectiveness, rebleeding rates, and safety profiles. Results were further stratified based on study design and clinical context (spontaneous versus iatrogenic epistaxis).

RESULTS AND DISCUSSION

Results

1. Study Selection and Identification

The study selection process is illustrated in the PRISMA flow diagram (Figure 1). A total of 44 records were identified through database searching, including 6 from PubMed, 38 from Google Scholar, and none from Cochrane. After removal of 5 duplicate records, 39 studies remained for title and abstract screening. Of these, 32 records were excluded based on lack of relevance to the study objectives. The full texts of 7 articles were assessed for eligibility, all of which were successfully retrieved. Following full-text evaluation, 2 studies were excluded for not meeting the predefined inclusion criteria. Ultimately, 5 studies were included in the final qualitative synthesis.

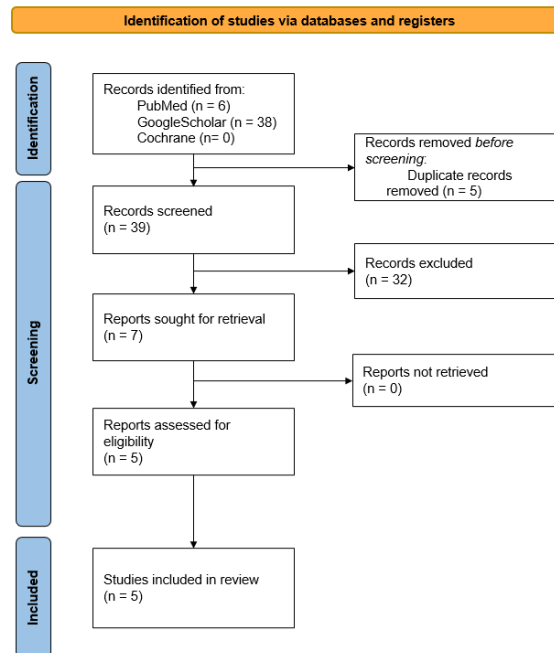


Figure 1. PRISMA Flowchart

2. Risk of Bias Assesment

The overall methodological quality of included studies was moderate to low. One randomized controlled trial and one large cohort study demonstrated low to moderate risk of bias, primarily due to unclear blinding and potential confounding. The remaining studies were case series, inherently associated with high risk of selection bias and lack of comparator groups. Consequently, the overall level of evidence remains limited and predominantly observational. Reviewers concluded that the data were appropriate enough for this analysis.

3. Summary of the Included Studies

A total of five studies were included in this review, comprising two retrospective cohort studies, one randomized controlled trial, and two case series (one prospective multicenter and one retrospective). The studies were conducted across the United States and Australia and included a total of 1,298 patients with either spontaneous or iatrogenic epistaxis, predominantly in postoperative settings. Sample sizes ranged from 22 to 985 participants. All studies evaluated topical application of RADA-16 hydrogel, either as a standalone intervention or compared with conventional management or alternative hemostatic agents. Overall, RADA-16 demonstrated consistent hemostatic effectiveness across studies, with reported success rates as high as 98.2% and significantly reduced postoperative bleeding compared to standard care in cohort data. In addition, several studies reported secondary benefits, including reduced adhesion formation and improved intraoperative visualization. The randomized controlled trial showed comparable hemostatic efficacy to a chitosan-based polymer, with significantly improved patient comfort during postoperative care. Table 1 displays the studies that were included.

Table 1. Summaries Included Studies

No.	First Author and Year	Study Design	Sample Criteria	Sample Size	Intervention Arms	Result
1.	Adelman et al., (2025)	Retrospective cohort study	Adults (18+) with hereditary hemorrhagic telangiectasia (HHT) and epistaxis	22 patients (26 applications)	Nasal RADA16 hydrogel	Epistaxis Severity Score (ESS) decreased by an average of 2.0 ; the treatment is safe for outpatient use without serious adverse effects.
2.	Soodin et al., (2022)	Prospective multicenter case series	Patients undergoing endonasal surgery (turbinate reduction, septoplasty, FESS)	167 patients	RADA16 2.5% (PuraStat)	Hemostatic efficacy reached 98.2% ; low incidence of adhesions (4.2%); transparent product facilitates visualization.
3.	Friedland et al., (2022)	Retrospective chart review (Case series)	Patients undergoing FESS (complete or limited)	94 patients	PuraStat (RADA16) in the absence of nasal packing	Effective in achieving hemostasis and reducing adhesion formation; only 4.25% of patients required additional treatment for bleeding.
4.	Xu et al., (2025)	Retrospective cohort study	Patients undergoing inferior turbinate submucosal resection (ITR)	985 patients (571 RADA16 group, 414 control group)	RADA16 vs. Non-RADA16	Risk of postoperative hemorrhage was significantly lower in the RADA16 cohort (0.35%) compared to the control group (2.17%).
5.	Hur et al., (2024)	Prospective, randomized, blinded trial (Inpatient-controlled)	Adults undergoing bilateral total ethmoidectomy for chronic rhinosinusitis	30 patients (60 ethmoid cavities)	RADA16 hydrogel (PuraGel) vs. Chitosan-based polymer (PosiSep X)	Significantly reduced pain during week 1 postoperative debridement; hemostatic efficacy was comparable to the chitosan polymer.

As presented in Table 1, the five included studies varied in study design, sample size, and methodological characteristics, which contributed to differences in their potential risk of bias. The methodological quality and risk of bias were assessed for each study using the appropriate Joanna Briggs Institute (JBI) critical appraisal tools according to study design. Adelman et al. (2025), a retrospective cohort study, had a low to moderate risk of bias, with the main concerns related to potential confounding and the retrospective nature of the data. Soodin et al. (2022) and Friedland et al. (2022), both case series, had a higher risk of selection bias due to the absence of comparator groups and the potential for incomplete representation of the target population. Xu et al. (2025), a large retrospective cohort study, demonstrated a relatively low to moderate risk of bias, although potential confounding and differences between the RADA-

16 and control groups could not be completely excluded. Hur et al. (2024), the randomized controlled trial, showed a relatively low risk of bias, although some methodological limitations, particularly related to blinding and its intrapatient-controlled design, were considered. Overall, the risk of bias varied across the included studies, with greater limitations observed in the observational case series. These limitations should be considered when interpreting the findings, particularly because most of the available evidence was derived from observational studies.

4. *Descriptive Analysis of RADA-16 Effectiveness and Clinical Outcomes*

The synthesis of the included studies demonstrates that RADA-16 self-assembling peptide hydrogel is a highly effective and safe intervention for achieving hemostasis and improving postoperative outcomes across a variety of endonasal procedures and conditions. The following analysis details its effectiveness in controlling hemorrhage, managing chronic epistaxis, and enhancing patient recovery.

Hemostatic Efficacy and Bleeding Control

RADA-16 has shown exceptional performance in achieving rapid hemostasis, particularly in surgical settings. In a large-scale retrospective cohort study of 985 patients undergoing inferior turbinate submucosal resection (ITR), the application of RADA-16 resulted in a significantly lower risk of postoperative hemorrhage (0.35%) compared to the control group (2.17%). Similarly, a prospective multicenter case series of 167 patients reported a hemostatic efficacy of 98.2%, with the hydrogel proving effective even in patients on anticoagulant medication. Furthermore, in the context of Functional Endoscopic Sinus Surgery (FESS), the use of RADA-16 allowed for the successful avoidance of traditional nasal packing, with only 4.25% of patients requiring additional intervention for bleeding (Soodin et al., 2022; Friedland et al., 2022).

Management of Chronic Epistaxis in HHT

Beyond acute surgical intervention, RADA-16 offers a novel conservative treatment for patients with Hereditary Hemorrhagic Telangiectasia (HHT). A cohort study involving 22 HHT patients demonstrated that nasal application of the hydrogel significantly decreased the Epistaxis Severity Score (ESS) by an average of 2.0 (see Figure 2). This reduction is 2.8 times the minimal clinically important difference, indicating a substantial improvement in the patients' quality of life (Adelman et al., 2025). The treatment was safely administered in an outpatient setting without the need for local anesthesia or an operating suite. As shown in Figure 3, here is the pre- and post-application appearance of RADA-16.

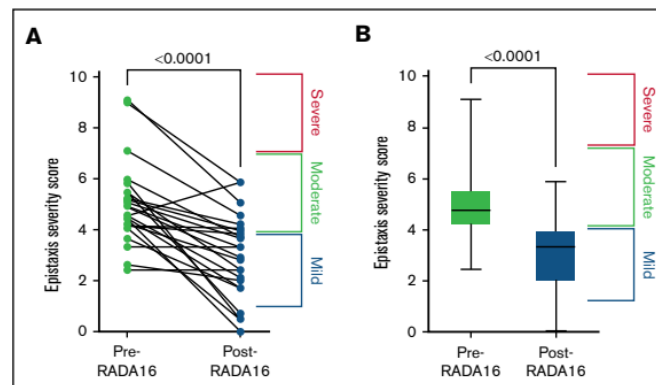


Figure 2. Decreased ESS score post-RADA16 (Adelman et al., 2025)

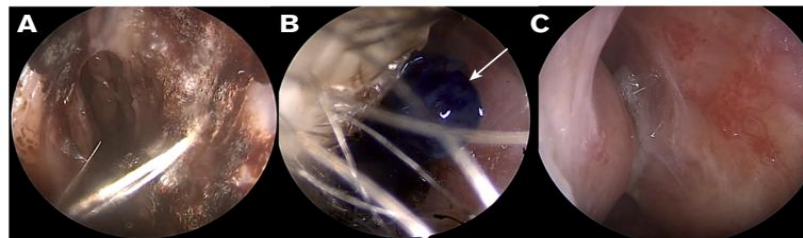


Figure 3. Nasal mucosa pre- and post-RADA-16 application in an HHT patient's right nasal cavity. (A) Baseline crusting and inflammation from HHT-related epistaxis. (B) Targeted application of RADA-16 hydrogel, mixed with methylene blue for visibility (arrow). (C) Follow-up assessment showing restored mucosal moisture and complete resolution of inflammation and crusting (Adelman et al., 2025).

Postoperative Recovery: Pain and Adhesion Formation

RADA-16 significantly enhances the postoperative experience by reducing debridement-related pain and minimizing scarring. A prospective, randomized, blinded trial found that patients treated with RADA-16 reported significantly less pain during their week 1 postoperative debridement compared to those treated with a chitosan-based polymer. The median pain score for the hydrogel was 4, compared to 5 for the control side. Regarding structural outcomes, RADA-16 is associated with low rates of adhesion (synechiae) formation. In multicenter surgical cohorts, the incidence of adhesions requiring treatment was as low as 4.2%. In FESS patients, while some minor adhesions occurred (24.47%), they were predominantly thin and easily divided via suction or scissors in an outpatient setting, with no patients requiring revision surgery for scarring (Hur et al., 2024; Xu et al., 2025).

Safety and Practical Advantages

Across all studies, RADA-16 maintained a high safety profile with no serious adverse effects, allergic reactions, or infections directly attributed to the product. The most common minor side effect was short-term, self-resolving nasal congestion. From a surgical standpoint, the transparency of the hydrogel provides a distinct advantage, as it allows clinicians to maintain a clear view of the treated surfaces and visualize potential bleeding sites after application. Additionally, the prefilled syringe delivery system makes the intervention convenient and easy to apply for clinicians (Hur et al., 2024).

Discussion

This systematic review explores the safety and efficacy of RADA-16, a self-assembling peptide hydrogel, for managing nosebleeds across various rhinologic contexts—specifically post-surgical bleeding and complications from Hereditary Hemorrhagic Telangiectasia (HHT). Epistaxis remains a significant challenge in otolaryngology, often straining healthcare resources and impacting patient well-being. This is especially true for those with HHT, where over 90% of patients face recurrent, sometimes life-threatening, spontaneous bleeding. Similarly, managing hemorrhage after procedures like FESS or septoplasty is critical, as these complications frequently lead to unplanned readmissions and secondary surgeries (Friedland et al., 2022; Xu et al., 2025).

The five studies analyzed here consistently show that RADA-16 significantly reduces the severity of epistaxis, postoperative bleeding rates, and the formation of adhesions (Pak et al., 2024). For instance, noted a 2.0-point drop in the Epistaxis Severity Score (ESS) among HHT patients nearly triple the minimum clinically important difference after outpatient application (Adelman et al., 2025). Much lower hemorrhage rate in the RADA-16 group compared to controls (0.35% vs. 2.17%) after turbinate surgery (Xu et al., 2025). Furthermore, high success rates in stopping bleeds (98.2% and 95.74%, respectively) across diverse surgical cases. These findings indicate favorable hemostatic outcomes across different patient groups and clinical settings, although the strength of this evidence varies according to study design and the presence of comparator groups (Soodin et al., 2022; Friedland et al., 2022).

Within rhinology specifically, the present review builds on earlier evidence from Lee et al. (2017), who reported zero rebleeding and adhesion formation in 60 patients undergoing endonasal turbinate reduction. However, these findings were generated from a single-arm cohort without a comparative group, limiting the strength of the evidence (Lee et al., 2017). The current evidence base extends this foundation by including larger and more heterogeneous populations, although it remains predominantly observational.

A key advantage of RADA-16 relative to conventional hemostatic agents lies in its synthetic, plasma-derivative-free composition: unlike thrombin-containing agents such as FloSeal®, it carries no risk of blood-borne pathogen transmission or immunogenic reaction (Soodin et al., 2022; Subramaniam et al., 2021). Its transparency during application is consistently rated as a clinically meaningful benefit by surgeons, allowing unobstructed visualization of the operative field a property particularly advantageous in narrow endonasal spaces (Soodin et al., 2022; Wong et al., 2020). Furthermore, as demonstrated by Adelman et al. (2025), its topical, outpatient applicability without the need for local anesthesia or an operating suite distinguishes it from more invasive procedural alternatives such as cautery, laser ablation, or septodermoplasty, all of which carry risks of further telangiectasia formation, thermal injury, or septal perforation (Adelman et al., 2025).

These conventional approaches have also been evaluated against other interventions in HHT-related epistaxis. Woodard et al. (2022), for example, reported that patients treated with sodium tetradecyl sulfate sclerotherapy required fewer procedures over 24 months than those treated with cautery or laser, with lower rates of nasal crusting, foul odor, and septal perforation. Other medical therapies have produced mixed findings. The NOSTRIL randomized placebo-controlled crossover trial found no significant reduction in the primary measures of epistaxis frequency, duration, or Epistaxis Severity Score with doxycycline, although exploratory longitudinal analyses suggested possible reductions over time (McWilliams et al., 2022).

Similarly, evidence for topical tranexamic acid has been synthesized in a systematic review and meta-analysis, supporting its consideration as a topical hemostatic approach for acute epistaxis (Gottlieb et al., 2019). In HHT specifically, a randomized clinical trial of intranasal bevacizumab found no significant reduction in epistaxis duration compared with placebo during the three months following treatment, illustrating the variable efficacy of pharmacological approaches (Dupuis-Girod et al., 2016). More recently, pomalidomide was evaluated in a randomized, placebo-controlled trial and was associated with a reduction in epistaxis severity in patients with HHT, although treatment-related adverse effects remain relevant when considering systemic therapy (Al-Samkari et al., 2024). These findings provide an important clinical context for interpreting RADA-16, as existing approaches differ substantially in mechanism, invasiveness, efficacy, safety profile, and quality of supporting evidence.

However, the available evidence also highlights meaningful limitations. Direct comparisons with other bioresorbable agents such as chitosan-based polymers or gelatin-thrombin combinations remain sparse; the only head-to-head randomized controlled trial, evaluated postoperative pain as its primary endpoint rather than hemostatic efficacy, finding no significant difference between RADA-16 and chitosan-based polymer in bleeding severity or mucosal healing scores (Hur et al., 2024). Moreover, the precise duration of RADA-16's persistence on nasal mucosa in the warm, moist sinonasal environment remains incompletely characterized (Adelman et al., 2025), and placebo-controlled data are entirely absent from the current rhinologic evidence base (Gelain et al., 2021; Lee et al., 2019).

RADA-16 is a fully synthetic 16-unit oligopeptide composed of four repeating amino acid sequences arginine (R), alanine (A), aspartic acid (D), and alanine (A) that spontaneously self-assembles into a three-dimensional nanofiber hydrogel scaffold upon exposure to physiological fluids such as blood or tissue fluid (Soodin et al., 2022; Hur et al., 2024). This assembly process is driven by ionic neutralization of the peptide's acidic solution upon contact with blood at physiological pH, resulting in rapid gelation occurring in under 15 seconds that is entirely independent of the patient's coagulation status (Sankar et al., 2021). The resulting hydrogel forms a transparent, biocompatible physical barrier directly over the bleeding vessel or mucosal surface, mechanically obstructing blood flow while simultaneously promoting coagulation in the adjacent vascular wall. Its architecture closely resembles the extracellular matrix of human tissue, facilitating cellular adhesion, migration, and mucosal regeneration properties that underpin its capacity to promote wound healing beyond mere hemostasis (3-D Matrix Europe SAS, 2019; Hur et al., 2024; Xu et al., 2025).

In the context of HHT-related epistaxis, the proposed mechanism is further multifactorial: by maintaining nasal moisture and creating a protective barrier over fragile telangiectasias, RADA-16 is thought to reduce crusting and air-induced mechanical stress two key precipitants of hemorrhage in this population (Wirsching et al., 2017). Following application, the hydrogel is gradually resorbed via enzymatic action within approximately 30 days, without the swelling capacity that characterizes some alternative agents, making it suitable for use in proximity to fragile anatomical structures (Soodin et al., 2022). Regarding safety, the reviewed studies consistently report a favorable adverse event profile. No serious complications attributable to RADA-16 were reported across any of the five included studies. The most commonly noted adverse effect was transient nasal congestion, observed in a subset of HHT patients, which resolved spontaneously within hours and did not prevent treatment continuation (Adelman et al., 2025). RADA-16 significantly reduced pain during postoperative

debridement compared to chitosan-based polymer, middle turbinate lateralization a theoretical risk when the hydrogel's thin application does not mechanically stabilize turbinate position was not formally assessed as an outcome in their trial, representing a safety gap requiring further investigation (Hur et al., 2024).

Beyond its primary hemostatic function, several secondary findings across the reviewed studies highlight RADA-16's broader clinical utility and potential to reshape postoperative rhinologic care pathways. Notably, Hur et al. (2024) the only randomized controlled trial included in this review demonstrated that RADA-16 was associated with significantly lower patient-reported pain during first-week postoperative debridement compared to a chitosan-based polymer (median score 4 vs. 5, $p = 0.015$), a finding with meaningful implications for patient compliance and satisfaction, given that pain during debridement has been documented as a contributor to missed postoperative appointments (Hur et al., 2024; Green et al., 2015). This pain-reducing effect is hypothesized to arise from the hydrogel's thin mucosal seal, which shields regenerating epithelium from airflow-induced desiccation a mechanism analogous to, but less obstructive than, cotton ball nasal occlusion (Kim et al., 2019).

From a health economics perspective, Xu et al. (2025) estimated the average epistaxis-related cost per patient at \$379.74 in the RADA-16 group compared to \$436.21 in the non-RADA-16 group; while this difference did not reach statistical significance ($p = 0.36$), the trend suggests that RADA-16 application may be cost-neutral or modestly cost-saving when reductions in emergency department visits and intervention requirements are factored in (Xu et al., 2025). Furthermore, Soodin et al. (2022) reported high surgeon satisfaction scores for RADA-16 across multiple dimensions including overall performance (4.6/5), ease of use (4.7/5), and transparency benefit (4.7/5) indicating strong real-world clinical acceptability. Taken collectively, these findings support RADA-16's role as a conservative, outpatient-compatible intervention that can be positioned early within the escalating treatment algorithm for epistaxis management particularly in HHT, where it may be offered prior to more invasive procedural approaches and as a routine adjunct in endonasal surgery to reduce postoperative morbidity, nasal packing dependency, and healthcare burden (Michaels et al., 2024; Soodin et al., 2022).

This review offers a broader perspective from the inclusion of studies spanning a range of clinical contexts disease-related epistaxis in HHT, postoperative bleeding following FESS, turbinate reduction, and ITR thereby providing a broader view of RADA-16's applicability than any single study could offer in isolation. The largest included study enrolled 985 patients across two surgical sites, affording relatively robust statistical power for its primary hemorrhage outcome, while the only RCT provides the highest level of internal validity within the current evidence base through its inpatient controlled, randomized, blinded design (Hur et al., 2024; Xu et al., 2025).

However, the significant methodological flaws across the included studies mean that any conclusions must be interpreted with caution. Since four out of the five studies relied on a retrospective design, the findings are particularly susceptible to selection bias, confounding variables, and errors in how outcomes were recorded. These inherent limitations ultimately weaken the overall certainty of the evidence presented. Sample sizes across most studies were small particularly in Adelman et al. (2025) with only 22 patients and 26 RADA-16 applications severely limiting statistical power and generalizability (Adelman et al., 2025). Notably, three of the five studies involved investigators with declared financial relationships with the manufacturer of RADA-16 (3-D Matrix), raising the possibility of reporting bias.

The absence of placebo or untreated control groups in all disease-related epistaxis studies prevents attribution of observed improvements solely to RADA-16, particularly given that the Epistaxis Severity Score used as the primary outcome in Adelman et al. (2025) has been associated with a clinically significant placebo effect in prior HHT research (Adelman et al., 2025). The lack of uniform definitions for hemorrhage and adhesion outcomes prevented any formal meta-analysis and made it difficult to compare results across the board. Furthermore, since most follow-up periods were limited to just two to six weeks, we still don't know how well RADA-16 holds up for long-term mucosal healing. To truly define its place in clinical guidelines, future research needs to focus on large-scale, prospective, and placebo-controlled trials that use standardized metrics and longer observation periods (Lee et al., 2023; Michaels et al., 2024).

CONCLUSION

Overall, the available evidence suggests that RADA-16 self-assembling peptide hydrogel has potential as a hemostatic option for managing epistaxis in both surgical and clinical settings. The included studies generally reported favorable outcomes, including effective bleeding control, reduced postoperative bleeding, and improvements in selected patient-related outcomes. Its transparency and ease of application may also provide practical advantages in clinical use, particularly in postoperative care and outpatient management. However, these findings should be interpreted cautiously because the available evidence remains limited and heterogeneous, with most studies using observational designs and relatively small or clinically specific populations.

Further research is needed to establish the effectiveness and safety of RADA-16 more definitively across different epistaxis settings. Future studies should prioritize well-designed, adequately powered randomized controlled trials with appropriate comparator groups and standardized definitions of hemostatic success, rebleeding, and adverse events. Longer follow-up periods are also needed to clarify the durability of hemostatic effects, long-term rebleeding rates, and safety outcomes. Such evidence would strengthen the certainty of current findings and help determine the appropriate clinical role of RADA-16 in the management of epistaxis.

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Conflict of Interest

The authors declare no conflict of interest.

Availability of Data and Materials

All data sources described in this study are directed at the corresponding author.

Ethics Approval and Consent to Participate

No human subjects are in this article, and informed consent is not applicable.

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