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ORIGINAL ARTICLE

Deliberations of the Safety Task Force: Risk factors and treatment of adverse events associated with aesthetic injectables

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Abstract

Background: The growing popularity of aesthetic procedures involving fillers, biostimulators, and neurotoxins has prompted concerns about patient safety. To address these concerns, a global Safety Task Force (STF) was formed.

Aims: The inaugural STF meeting prioritized vascular compromise prevention and management, guiding clinical trial design and materials for future meetings, and collecting data from experts on current safety methods.

Methods: The STF was formed and consisted of 16 experts from nine different countries, with each possessing distinct expertise in various fields related to aesthetic injectables. Current safety data, protocols, knowledge gaps and future research priorities were discussed and voted upon.

Results: The establishment of a global database for tracking filler-related AEs was favored by 93% of participants. Discussions revolved around the database's scope, data standardization, and whether non-medical contributors should be included. Aspiration as a safety technique garnered support from 73% of participants. Approximately 43% of participants incorporate ultrasound in their injections, with divergent opinions on its impact and potential when used as a standard of practice versus in AE management. Most physicians on the task force incorporated cannula use for some of their injections (93%). There were varying perspectives on treatments for vascular adverse events (VAE), the primary causes, and the adoption of new protocols in the field.

For affiliations refer to page 3563.

Conclusions: The STF meeting underscored the need for a coordinated effort to address complications related to HA fillers, including VAE management and hyaluronidase protocols. Reliable treatment endpoints were evaluated, but improved measurement methods are needed. Future meetings will focus on addressing delayed complications, furthering safety in this field.

KEYWORDS
consensus, expert opinion, hyaluronic acid fillers, neurotoxins, pharmacovigilance

1 | INTRODUCTION

Over the last decade, the number of patients seeking minimally invasive aesthetic procedures has continuously increased each year.[1] This can be partially attributed to the expanding array of treatment options available for individuals seeking to enhance their appearance.[2] For example, the use of injectables such as hyaluronic acid (HA) fillers, biostimulators, and neurotoxins are commonly indicated to restore volume to the face, produce more collagen, and reduce the appearance of fine lines and wrinkles.[1] These products provide minimally invasive solutions to address a wide spectrum of aesthetic concerns.[3]

Given the continual introduction of new products, techniques, and indications, physicians as well as other health care practitioners are continuously working to improve patient safety. While many clinical trials have evaluated the safety and effectiveness of injectables, and these products are generally categorized as low risk, various AEs have been associated with these products, including rare severe AEs (e.g., blindness, stroke).[4] Nevertheless, lack of uniform decision making and expert recommendations highlight the necessity of standardized approaches to complication management.

Recognizing the importance of understanding the safe and effective management of AEs associated with injectable procedures, the Safety Task Force (STF) was established; a group of experienced physician global thought leaders and experts in the field of aesthetics who gathered with the objective of developing, without direction from an industry Sponsor, standardized approaches to the prevention and management of AEs related to aesthetic injections. This endeavor is driven by the intention to address existing gaps in the academic literature and to establish consistent safety protocols that can be applied across different geographical regions. The STF's primary goal is to consolidate existing knowledge, reduce research redundancy, promote a unified approach to the prevention and management of AEs as well as guide future directions in research to help answer questions and optimize treatment protocols.

Herein, we report the results of the STF's inaugural meeting. The objectives of the first meeting were: to prioritize and discuss topics related to AE management and prevention, to guide future STF meetings, data generation, and guideline development; to understand which topics related to AE management and prevention were most relevant based on the experts opinions; to prioritize key topics and discuss them at a high-level using survey questions to guide the discussion; to identify the topics ranked as the highest priority for in depth discussion in a future meeting and identification of opportunities for medical communications activities that may contribute to the safe use of fillers in the wider aesthetics community.

2 | METHODOLOGY

2.1 | Working group overview

The STF committee included 16 distinguished experts from nine different countries, each possessing valuable insight in various aspects related to aesthetic injectables. Collectively, these experts represented: Australia, Austria/Germany, Brazil, Canada, China, France, the Netherlands, South Korea, and the United States (Figure 1). Comprising eight dermatologists, six plastic surgeons, one anatomist, and one phlebologist; the panelists were selected through a systematic process that took into consideration their specific domain expertise, geographic diversity, scholarly contributions, and professional affiliations.

2.2 | Meeting agenda

The meeting consisted of three presentations, each of which explored one key theme identified prior to the meeting. These included an overview of (I) challenges in injectables research, (II) historical perspectives on managing AEs, and (III) most recent advancements in the treatment and management of vascular AEs (VAEs). Following a discussion period, a survey was implemented (Table 1) with the intention of attaining a consensus on requisite measures and prospective directives. Overviews of the presentations and the survey responses are presented below:

3 | RESULTS AND DISCUSSION

3.1 | Challenges in injectables research: AE underreporting

There is a growing body of evidence regarding AEs associated with HA fillers. A PubMed search conducted in September 2023, using the terms "Complications hyaluronic acid fillers," identified

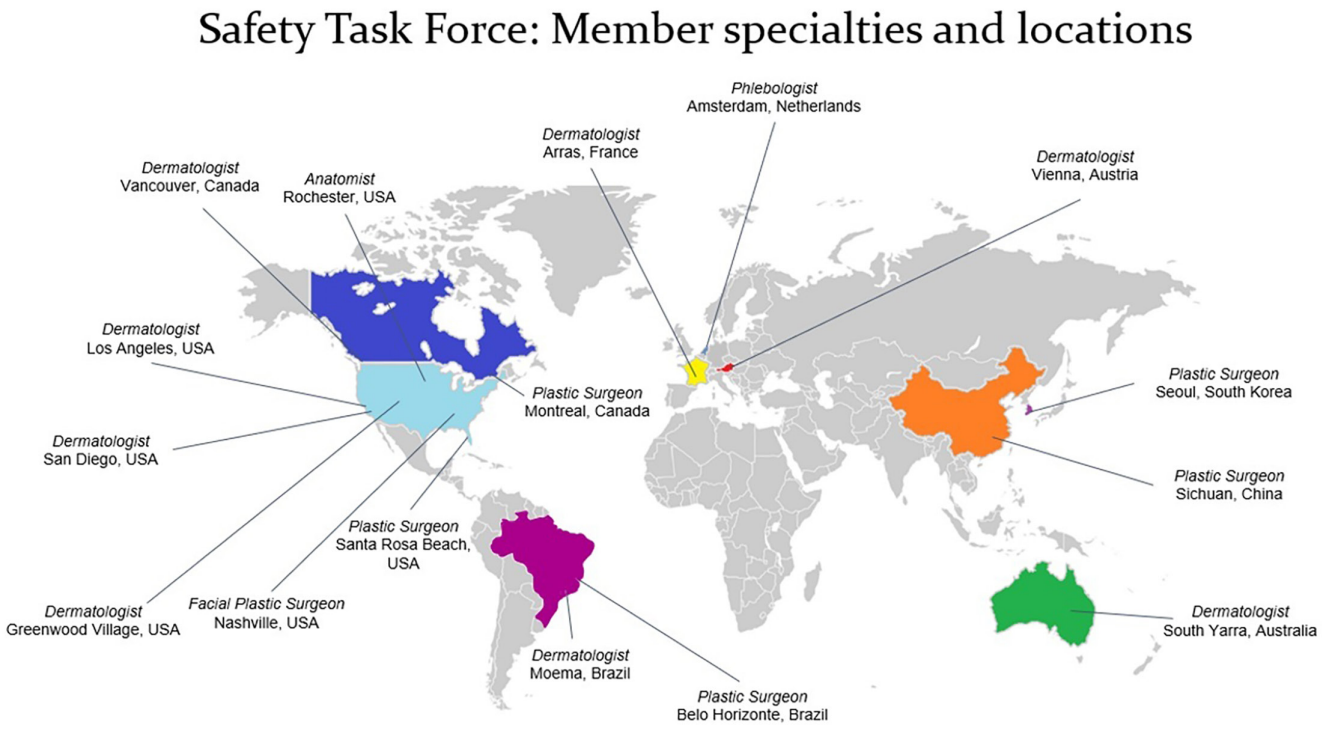

FIGURE 1 Medical specialties and geographical locations of the panelists.

333 research articles published between 2000 and 2018 that discussed HA filler complications. Likewise, from 2019 to 2023 there were 408 articles published on this topic, indicating a notable increase in research efforts in the last 5 years, compared to the preceding 18 years. Despite the increase in publications that have generated an abundance of data, it has also exacerbated and diluted the prevailing lack of consensus and clarity on various aspects of aesthetic injections. Moreover, a significant majority of articles offered a low level of evidence (e.g., case reports/series, anecdotal reports).

In a 2002 study, a retrospective (1999–2000) review of worldwide (Europe, Canada, Australia, South America, and Asia) data collected by the manufacturer of NASHA (nonanimal stabilized hyaluronic acid), it was revealed that there were 222 AEs documented among an estimated 144 000 patients treated in 1999, indicating an incidence of 1/1400 patients. The following year, a similar assessment revealed an AE incidence rate of 1/1800 patients.[5]

Daines and colleagues (2013) published a retrospective analysis of AE data from a single aesthetic center in California with two physician injectors, covering the years 2007 to 2011. Their results revealed an approximate AE incidence rate of 1/149 procedures.[6] In another study, published in 2015, 23 doctors from eight United States clinics reported AEs related to injectable procedures from March to December 2011. Their results revealed an AE incidence rate of 1/425 injections.[7] In interpreting these results, it is important to understanding that inclusion criteria and definitions of AEs vary by authors.

A 2018 study reviewed AEs reported to the United States' Manufacturer and User Facility Device Experience (MAUDE) database between 2007 and 2017. This database consists of a passive surveillance system designed to monitor device performance and identify potential safety concerns associated with medical devices. The study revealed an AE incident rate of only 1/3600 procedures (0.027%).[8] The complexity of reporting, managing, and follow-up of AEs within the field of aesthetics is compounded by concerns about litigation, often discouraging the reporting of complications and contributing to underreporting incidents in national databases.[9]

The increased research into HA filler complications has emphasized the critical need to re-evaluate safety reporting procedures. In 2021, Enright et al., published an article where they analyzed Health Canada's national reporting database, MedEffect™. Covering data which expanded 53 years, the analyses examined 1459 individual reports, totaling 5714 AEs. Notably, nearly all AEs (99.84%) were associated with neurotoxins, with only one report associated with soft tissue fillers.[4] This portrayal implies an overly favorable and lopsided filler safety perception. Yet, drawing conclusions from this data could mislead perceptions of approved products' safety and efficacy in Canada. While AE reactions with these products are rare, the infrequent reporting to MedEffect™ may not truly represent their real-life incidence rates.

In 2022, a similar review of the United State's MAUDE database was published. This study evaluated post-market data for delayed (≥14 days post-treatment) AEs, including inflammatory and noninflammatory nodules, hypersensitivity reactions, and granulomas, for HA fillers approved by the FDA between 2016 and 2020. Of the 585 reports evaluated, 195 (33.3%) included delayed AEs of interest. Of those, 71.8% related to nodules (42.1% inflammatory and 29.7%

TABLE 1 Questions asked of the panelists, relating to adverse events in the aesthetics field.

Global database							
Is there a need for a global database of AEs? ($n=15$)							
Agree			Disagree				
93% ($n=14$)			7% ($n=1$)				
Should this database incorporate: ($n=15$)							
Neuromodulators	HA fillers		Biostimulators		Other Fillers		All the above
0	20% ($n=3$)		6% ($n=1$)		0		73% ($n=11$)
Should this database be: ($n=15$)							
Completely anonymous	Anonymous but localized by country/ region specific		Anonymous but clinic specific:		Not anonymous		
0	73% ($n=13$)		0		26% ($n=2$)		
Should the database incorporate all toxins and fillers regardless of company, or should it be company specific? ($n=15$)							
All companies			Specific sponsor				
100% ($n=15$)			0				
Aspiration							
Is aspiration a valid test? ($n=15$)							
Yes			No				
73% ($n=11$)			26% ($n=4$)				
How long is needed for an aspiration test to be valid? ($n=15$)							
3 s	5 s		7 s		10 s		I do not believe in aspiration
0	13% ($n=2$)		20% ($n=3$)		53% ($n=8$)		13% ($n=2$)
Are unprimed needles required for performing aspiration? ($n=12$)							
Yes	No		Indifferent		I do not believe in aspiration		
17% ($n=2$)	75% ($n=9$)		0		8% ($n=1$)		
Do you recommend aspiration in soft tissue? ($n=15$)							
Yes		No			I do not believe in aspiration		
60% ($n=9$)		27% ($n=4$)			13% ($n=2$)		
What anatomic areas are best for aspiration? **Panelists had the option to vote for multiple areas*							
Temple	Nose	Deep pyriform space	Chin	Tear through	NLF	Jawline	I do not believe in aspiration
53% ($n=8$)	40% ($n=6$)	80% ($n=12$)	33% ($n=5$)	13% ($n=2$)	27% ($n=4$)	13% ($n=2$)	13% ($n=2$)
Ultrasound							
Do you use ultrasound in conjunction with your injections? ($n=14$)							
Yes			No				
43% ($n=6$)			57% ($n=8$)				
Does ultrasound lead to safer injections? ($n=15$)							
Yes			No				
47% ($n=7$)			53% ($n=8$)				
In what areas is ultrasound used? **Panelists had the option to vote for multiple areas*							
Temple	Nose	Cheek	Tear trough	Deep pyriform	Chin	Jawline	
67% ($n=10$)	33% ($n=5$)	27% ($n=4$)	13% ($n=2$)	73% ($n=11$)	20% ($n=3$)	27% ($n=4$)	
Do you feel ultrasound is the current standard for complication management? ($n=15$)							
Yes			No				
47% ($n=7$)			53% ($n=8$)				

TABLE 1 (Continued)

Do you feel pretreatment ultrasound will be the standard prior to filler injections within ten years? ($n=14$)								
Yes				No				
43% ($n=6$)				57% ($n=8$)				
Do you feel pretreatment ultrasound will be the standard for management of filler complication within ten years? ($N=13$)								
Yes				No				
69% ($n=9$)				31% ($n=4$)				
Cannulas vs needles								
Do you use cannulas in your practice? ($n=14$)								
Yes				No				
93% ($n=13$)				7% ($n=1$)				
Do you believe cannulas are safer than needles? ($n=14$)								
Yes				No				
71% ($n=10$)				29% ($n=4$)				
What is your standard cannula size for most areas? ($n=10$)								
22G	23G			25G		27G		
60% ($n=6$)	10% ($n=1$)			30% ($n=3$)		0		
What gauge cannula do you use for injecting the temporal region? ($n=13$)								
22G	23G			25G		27G		
69% ($n=9$)	8% ($n=1$)			23% ($n=3$)		0		
What areas are best for cannulas? **Panelists had the option to vote for multiple areas*								
Temple	Forehead	Nose	Cheek	Tear through	Lips	NLF	Chin	Jawline
60% ($n=9$)	80% ($n=12$)	20% ($n=3$)	67% ($n=10$)	80% ($n=12$)	20% ($n=3$)	67% ($n=10$)	27% ($n=4$)	73% ($n=11$)
Is a larger needle size safer than a smaller needle? ($n=15$)								
Yes				No				
25% ($n=4$)				75% ($n=11$)				
Vascular adverse events								
In addition to hyaluronidase, which of the following are useful for managing VAE?								
*Panelists had the option to vote for multiple options								
Nitroglycerin	Aspirin	Lidocaine	Heparin	Steroids	Exosomes	Hbo or oxygen therapy		
33% ($n=5$)	67% ($n=10$)	6% ($n=1$)	13% ($n=2$)	40% ($n=6$)	6% ($n=1$)	67% ($n=10$)		
In treating non-HA related VAE, is hyaluronidase used? ($n=15$)								
Yes				No				
60% ($n=9$)				40% ($n=6$)				
Is ultrasound useful in the management of VAEs? ($n=15$)								
Yes				No				
100% ($n=15$)				($n=0$)				
Can select VAEs be treated with observation, heat, massage, and aspirin (without hyaluronidase)? ($n=15$)								
Yes				No				
33% ($n=5$)				67% ($n=10$)				
Intraluminal vs extraluminal								
Does external compression of an artery cause VAE (nasal tip excluded)? ($n=15$)								
Yes				No				
13% ($n=2$)				87% ($n=13$)				
Does external compression of an artery cause VAE is nasal tip? ($n=14$)								
Yes				No				
64% ($n=9$)				36% ($n=5$)				

(Continues)

TABLE 1 (Continued)

Is intraluminal injection of filler the primary cause of VAE? ($n=14$)			
Yes		No	
86% ($n=12$)		14% ($n=2$)	
Can venous VAE be caused by either intraluminal or extraluminal compression? ($n=14$)			
Yes		No	
64% ($n=9$)		36% ($n=5$)	
Clinical end points			
Please rank the best endpoints for treating VAE:			
1st	2nd	3rd	4th
Skin condition and color	Capillary refill	Pain	Ultrasound findings
Is there a need to have a better way to measure endpoints? ($n=14$)			
Yes	No		
64% ($n=9$)	36% ($n=5$)		
Hyaluronidase protocol			
Is DeLorenzi's 25 high-dose protocol considered the gold standard for VAE? ($n=14$)			
Yes		No	
93% ($n=13$)		7% ($n=1$)	
How long do you need to wait between doses of hyaluronidase? ($n=14$)			
5 min	10 min	30 min	60 min
0	27% 4	64% 9	7% 1
Do you perform skin test prior to hyaluronidase injection? ($n=14$)			
Yes		No	
7% ($n=1$)		93% ($n=13$)	
Are ultrasound-guided injections more efficient at confirming the treatment of a VAE? ($n=13$)			
Yes		No	
77% ($n=10$)		23% ($n=3$)	
Should the new protocol by the Cutaneous Group[27] be adopted as the new standard? ($n=14$)			
Yes		No	
57% ($n=8$)		43% ($n=6$)	

Abbreviations: AEs, Adverse events; G, Gauge; HA, hyaluronic acid; Hbo, Hyperbaric oxygen; NLF, Nasolabial folds; VAE, Vascular adverse event.

noninflammatory), 21.5% to hypersensitivity reactions, and 6.7% to granulomas. The authors concluded that although delayed AEs are rare, a significant number of reports occurred for these events within a five-year timeframe.[10]

The disparity between data reported in academic research papers versus passive surveillance systems highlights a significant issue: the notable under-reporting of AEs. This challenge complicates efforts to thoroughly analyze and utilize data for real-world evidence translation. Moreover, it precedes the development and validation of treatment protocols and management strategies.[4] This situation underscores the crucial need for a centralized authority capable of offering guidance to minimize redundant research efforts.[3] Recognizing the value of collecting prospective data, there is growing recognition of the importance of analysis and measurement of AEs in fine tuning recommendations for avoiding, managing, and treating AEs.[6] The current knowledge base primarily consists of case reports and practitioner experiences, indicating the need for a more comprehensive approach.

The proposition of establishing a global AE database for aesthetic injectables aims to address these challenges. This database would systematically collect and analyze AE data worldwide, offering a platform for rapid identification of trends and enhancing our understanding of risks associated with different products and patient demographics. Additionally, it would facilitate collaboration among healthcare professionals, regulators, and researchers globally, ultimately supporting improved management of safety concerns in aesthetic procedures by enabling evidence-based protocols and more effective strategies.

3.1.1 | Global database: Survey response and discussion

Q1. Is there a need for a global database of AEs? (n = 15)

The discussion revolved around the idea of creating a global database for tracking AEs associated with aesthetic injectables.

Physician participants examined the practicality, necessity, and challenges associated with this concept. Concerns included the management of international data and whether non-medical contributors, like those from medical spas, non-physician "supervised" and unregulated centers, should be included. The conversation emphasized the importance of standardized data collection and consistent terminology/definitions across different markets to ensure a unified approach to understanding and addressing complications in aesthetic procedures. Notably, the discussion resulted in a substantial 93% consensus among participants ($n=14$), with a limited 7% ($n=1$) expressing reservations about the proposed initiative. In addition to these insights, the practical aspects of establishing such a global database were also considered, including the required financial investment, the need for standardized data, and the challenge of addressing underrepresented AEs from various sources. Accurate recognition and documentation of complications and the inclusion of different procedure types in the database were also discussed, reflecting the complexities of this endeavor.

Q2. What products should this database incorporate? (n = 15)

Initially, participants deliberated on the database's scope, considering whether it should include specific product categories like fillers, neuromodulators, and biostimulators or encompass all aesthetic products. The issue of threads was raised, with the consensus being to exclude them due to their distinct nature from injectables. While 73% ($n=11$) believed that all the mentioned injectables should be in the database, 20% ($n=3$) of the panelist voted for only HA fillers to be incorporated and 7% ($n=1$) voted to incorporate both HA fillers and biostimulators.

Q3. Should this database be anonymized? (n = 15)

A debate revolved around several critical aspects, including the level of anonymity within the database, the challenges in standardizing terminology for AEs, and the complexity of distinguishing between symptoms and diagnoses when reporting incidents. Additionally, there was contemplation regarding whether the initiative should be led by a single industry sponsor (as in this unrestricted grant setting), or if it would be more credible and impartial if overseen by an independent professional society or a collective of industry stakeholders. This discourse emphasized the significance of transparency, credibility, and impartiality in managing safety-related data in the field of medical aesthetics. Of the 15 voters, 87% ($n=13$) voted that this database should be anonymous but localized by country and region, and 13% ($n=2$) voted that the database should not be anonymous at all. None of the participants voted for a completely anonymous database.

Q4. Should the database incorporate all toxins and fillers regardless of company or should it be company specific? (n = 15)

There was a suggestion to explore the possibility of an independent body or professional organization/society overseeing such a database rather than industry sponsorship alone, as this would allow complete independence in what is evaluated and reported. The role of companies in managing safety databases was mentioned, along with the complexity of making causality assessments in a public database accessible to various stakeholders. All, 100% ($n=15$) of the experts voted for the database to incorporate all company's products.

4 | HISTORICAL PERSPECTIVES ON AE MANAGEMENT

As others have explored means of enhancing treatment safety through different approaches,[11] it is worth noting some techniques have been widely implemented and/or discussed to date. In this section, we provide brief descriptions of major safety initiatives and discuss benefits and/or limitations associated with their implementation.

4.1 | Aspiration: Background

Aspiration is a commonly employed safety measure where an injector pulls back on the syringe's plunger (typically for 5–10 s) and verifies if blood is drawn, which may indicate that the needle is placed within a vessel. Consequently, the needle tip requires repositioning in order to avoid vascular compromise.[12] However, the absence of blood during aspiration does not imply a needle is not within an artery.[13] Therefore, the utility of aspiration is subject to debate, and research indicates the presence of numerous contributing factors. The effectiveness of aspiration as a safety measure exhibits variability, contingent on factors such as the injection site, needle gauge, syringe dimensions, duration of pullback, the surface the needle tip is in contact with, and the patient's blood pressure.[12,13] Furthermore, external variables such as inadvertent needle displacement by the injector or patient movement can potentially alter the needle's trajectory, resulting in false results.

4.2 | Aspiration: Survey responses and discussion

4.2.1 | Q1. Is aspiration a valid test? ($n=15$)

A substantial majority, 73% ($n=11$) of respondents voted in favor of aspiration, while a minority of 26% ($n=4$) voted against it.

4.2.2 | Q2. How long is needed for the test? ($n=15$)

Survey results, 74% ($n=11$) of respondents advocated for pull back duration ≥7 s. Two (13%) advisors felt 2 s was long enough while two (13%) advisors reiterated that aspiration is not a valid test, thus, did not provide response.

4.2.3 | Q3. Are unprimed needles required? ($n = 12$)

Priming removes air from the needle. The majority 75% ($n = 9$) of participants agreed that aspiration could be performed with primed needles, while 17% ($n = 2$) reported that the use of unprimed needles is required for reliably performing aspiration. One advisor did not respond to the question but reiterated their skepticism regarding aspiration altogether.

4.2.4 | Q4. Do you recommend aspiration on bone? ($n = 15$)

Most advisors [80% ($n = 12$)], advocated for aspirating on bone (such as at the zygoma or temple).

4.2.5 | Q5. Do you recommend aspiration in soft tissue? ($n = 15$)

Nine (60%) participants endorsed the practice of aspirating in soft tissues, while 27% ($n = 4$) advised against it, and 13% ($n = 2$) held the view that aspiration is not a valid test.

4.2.6 | Q6. What anatomic areas are best for aspiration?

Anatomical sites found most suitable for aspiration included the deep pyriform area, temporal regions, nose, chin, nasolabial area, tear troughs, and jawline; but again, one advisor reiterated the lack of literature demonstrating aspiration improving safety outcomes.

4.3 | Cannulas versus needles: Background

In the aesthetics field, it is a commonly held belief that needles, while providing precision and control, carry a higher risk of injuring blood vessels or nerves—especially in sensitive areas when used for injecting soft tissue fillers. In contrast, cannulas are considered safer due to their blunt tips, which significantly reduce the risk of such injuries.[14] Additionally, it is worth noting that the safety considerations surrounding needles and cannulas may extend to their varying sizes.[15]

Observations have shown that cannulas of different sizes generally require greater force than needles to penetrate arteries or veins, with the exception of 27-gauge cannulas. This finding implies that both 22- and 25-gauge cannulas can be considered reasonably safe options when it comes to intraarterial penetration. However, when comparing the required forces for penetration between 27-gauge cannulas and needles, similar outcomes were observed. Consequently, there appears to be no significant difference in safety between using 27-gauge cannulas or needles within this context.[15] Except for 27-gauge cannulas, which performed similarly to 27-gauge needles, all other measured cannula sizes required greater forces for intraarterial penetration than their needle counterparts, affirming the safety of 22- and 25-gauge cannulas.[13]

4.4 | Cannulas versus needles: Survey responses and discussion

4.4.1 | Q1. Do you use cannulas in your practice? ($n = 14$)

The majority of respondents [93% ($n = 13$)] use cannulas in practice.

4.4.2 | Q2. Do you believe cannulas are safer than needles? ($n = 14$)

The majority of respondents [71% ($n = 10$)] believed cannulas are safer than needles. Although there was variability in the opinion of the panelists, most experts seem to agree that choosing cannulas is preferable due to concerns about VAE in at least some of the anatomic regions mentioned above.

4.4.3 | Q3. What is your standard cannula size for most areas? ($n = 10$)

In response to this question, a variety of preferences were indicated:

- Six (60%) participants favored a 22-gauge (G) cannula.
- Three (30%) participants recommended a 25G cannula.
- One (10%) participant reported majority use of a 23G cannula.

4.4.4 | Q4. What gauge cannula do you use for treating the temple? ($n = 13$)

Most respondents [75% ($n = 9$)] opted for a 22G cannula, 8% ($n = 1$) of participants favored a 23G, and 23% ($n = 3$) respondents preferred a 25G cannula.

4.4.5 | Q5. What areas are best for cannulas? ($n = 12$)

In response to this question, a variety of preferences were indicated, as follows:

- Temple: 9 votes (75%)
- Forehead: 12 votes (100%)
- Nose: 3 votes (25%)

- Cheek: 10 votes (83%)
- Tear trough: 12 votes (100%)
- Lips: 3 votes (25%)
- Nasolabial folds (NLFs): 10 votes (83%)
- Chin: 4 votes (33%)
- Jawline: 11 votes (92%)

4.4.6 | Q6. Is a larger needle size safer than a smaller needle? ($n = 15$)

The majority [73% ($n = 11$)] of respondents answered "No." This indicates that the prevailing perspective is that a larger needle size is not considered safer than a smaller one (although a 22G cannula may be considered safer than a 30G cannula).

4.5 | Hyaluronidase: Background

Hyaluronidase plays a pivotal role in dissolving HA based fillers, swiftly restoring blood flow, and mitigating vascular occlusion. The following overview highlights key findings and implications regarding the use of hyaluronidase in AE management and treatment:

4.5.1 | Hyaluronidase efficacy

Early (2005) reports of vascular compromise indicated the potential benefits of hyaluronidase injections when dealing with complications related to fillers. Since then, hyaluronidase has emerged as a pivotal tool in managing complications associated with HA fillers[16]

4.5.2 | Proximity and effectiveness

Intriguingly, there are instances where hyaluronidase injections administered near suspected occluded vessels have yielded positive outcomes. This suggests that "close is good enough," implying that hyaluronidase can effectively restore circulation, even when injected in proximity to, rather than directly into, occluded vessels[17]

4.5.3 | Cadaver studies on hyaluronidase

Cadaver studies, such as those conducted by DeLorenzi in 2014, provide valuable insights into how hyaluronidase interacts with HA fillers within vessels. These studies revealed that hyaluronidase can cross a cadaveric artery wall and then hydrolyze cross-linked HA within the intact facial artery.[18] This finding challenges the notion that direct intra-arterial injection is always necessary for restoring circulation, lending to the practice of diffusely injecting hyaluronidase into ischemic tissues when accidental intra-arterial injection occurs.[18] However, in a rabbit model, extravascular hyaluronidase was unable to penetrate the arterial lumen, so more research in this area is needed[19]

4.5.4 | Differentiating bruising and vascular compromise

It is essential to differentiate between bruising and vascular compromise. Bruising is characterized by a multifocal appearance, whereas vascular compromise manifests as a marbled, livedoid, and reticulated pattern and is often accompanied by pain. Distinguishing between these two conditions is critical for appropriate intervention and management. Distinct skin patterns are described to help recognize a vascular compromise.[20] Unfortunately, further bruising from punctures and hyaluronidase injections may mask the true nature of the discoloration.

4.5.5 | Consideration of patient factors

When addressing potential complications like necrosis, comprehensive risk assessment should consider patient-specific factors. These include adherence to pre-procedure instructions, current medications, and underlying medical conditions, all of which may contribute to the overall risk profile for AEs.

In summary, research has indicated the effectiveness of hyaluronidase even when it is injected near blocked blood vessel. Cadaver studies shed light on its interactions with HA fillers within vessels, providing support for a broader application beyond direct intra-arterial injection.[18] Different protocols cater to diverse clinical scenarios, and the ability to distinguish between bruising and vascular compromise is fundamental. Moreover, individual patient-specific variables play a pivotal role in risk assessment and management, accentuating the dynamic and evolving role of hyaluronidase in enhancing the safety and outcomes of aesthetic procedures involving HA fillers.

4.6 | Hyaluronidase: Survey responses and discussion

4.6.1 | Q1. Is DeLorenzi's high-dose protocol considered the gold standard for VAE? ($n = 14$)

The vast majority (93% [$n = 13$]) of respondents indicated that they consider DeLorenzi's high-dose protocol to be the gold standard for VAE.[21] Only 7% ($n = 1$) disagreed with this statement.

4.6.2 | Q2. How long do you need to wait between doses of hyaluronidase? ($n = 11$)

The advisors held different opinions regarding the length of time between doses of hyaluronidase:

- One (9%) participant indicated 1–60 min.
- Six (55%) participants recommended a wait time of 30 min.
- Four (36%) participants suggested a 10-min waiting period.

This trend demonstrates a preference for earlier and more frequent injections of hyaluronidase.

4.6.3 | Q3. Do you perform a skin test prior to hyaluronidase injection? ($n = 14$)

The majority of respondents [93% ($n = 13$)] reported that they do not perform a skin test prior to hyaluronidase injection but cited frequent use of human recombinant hyaluronidase as the reason why. Only a single responder [7% ($n = 1$)] using animal-derived hyaluronidase indicated that they perform a skin test prior to hyaluronidase injection.

4.7 | Necrosis: Background

In the context of complications arising from aesthetic procedures involving fillers, several cases have raised questions about the potential involvement of microcirculatory issues and vasospasm. In 2018, Han J et al., published a case report proposing that tissue necrosis in the glabella following HA injection may not solely result from intravascular injection or extravascular compression by HA filler. Instead, it was postulated that a disturbance in microcirculation due to persistent vasospasm, induced by the HA injection, might have contributed to this patient's condition.[22]

In a 2011 case report by Kang MS et al., skin necrosis in the nasal alar area, despite no direct filler injection to that area, was attributed to a sole arterial branch supplying blood to the nasal ala. Three Dimensional Computed Tomography (3D-CT) angiography showed compensatory collateral vessel dilation, suggesting localized skin necrosis resulted from intravascular embolization of the terminal-branch arteriole due to inadvertent intra-arterial filler injection.[23] In a 2009 study, the authors highlighted anatomical factors in facial tissue augmentation, prompting consideration of microcirculatory issues potentially causing vasospasm.[24]

The unique tissue damage patterns observed in these cases, extending beyond typical bruising, and often crossing embryonic fusion lines, raised intriguing questions. Could filler inadvertently enter a vessel, causing occlusion, or might excessive filler compress against underlying cartilage/bone, like the nose (especially in light of previous surgeries or scar tissue)? To enhance safety in aesthetic procedures, exploring novel approaches is imperative. Ultrasound imaging has emerged as a valuable tool for guiding hyaluronidase injections and identifying potential target areas. Researchers in this field believe in the significant potential benefits of ultrasound imaging for improving the precision and safety of dermal filler injections.[25] Ultrasound's effectiveness largely hinges on the operator's skill, which accounts for most of the initial resistance to its adoption. Learning and mastering ultrasound can take time, but the question as to whether it will lead to safer injections has yet to be answered.

4.8 | Intraluminal versus extraluminal: Survey response and discussion

4.8.1 | Q1. Does external compression of an artery cause VAE (nasal tip excluded)? ($n = 15$)

Among participants, the majority of respondents [87% ($n = 13$)] answered "No", while 13% ($n = 2$) of respondents answered "Yes." One panelist suggested that recent literature on artery transitions challenges this notion.[25]

4.8.2 | Q2. Does external compression of an artery cause VAE in the nasal tip? ($n = 14$)

Most respondents [64% ($n = 9$)] indicated that they believed external artery compression can lead to VAE in the nasal tip, while 34% ($n = 5$) of respondents disagreed, citing the use of cartilage graft in the tip rarely causes compression issues.

4.8.3 | Q3. Is intraluminal injection of filler the primary cause of VAE? ($n = 14$)

The majority of respondents, 86% ($n = 12$) believed intraluminal injection of filler to be the main and likely exclusive cause of VAE.

4.8.4 | Q4. Can venous VAE be caused by either intraluminal or extraluminal compression? ($n = 14$)

Most, respondents [64% ($n = 9$)] indicated that they believed VAE can result from both intraluminal and extraluminal compression, 36% ($n = 5$) did not consider both forms of compression as possible causes of venous VAE.

4.9 | Clinical endpoints: Survey response and discussion

4.9.1 | Q1. Rank the best endpoints in treating VAE

The advisors provided the following rank order for endpoints best suited for evidencing the treatment of VAE:

1. Skin condition and color
2. Capillary refill
3. Pain
4. Ultrasound findings

4.9.2 | Q2. Is there a need to have a better way to measure endpoints? ($n = 14$)

Most respondents [64% ($n = 9$)] believed there is a need for improved methods to measure endpoints.

4.10 | Ultrasound: Survey response and discussion

4.10.1 | Q1. Do you use ultrasound in conjunction with your injections? ($n = 14$)

The physician advisors had varied levels of experience implementing the use of ultrasound into their practices, with 43% ($n = 6$) incorporating the use of some form of ultrasound (including primary AE management) and 57% ($n = 8$) not utilizing ultrasound at all in practice. Of note, this observation may confound the survey responses to further questions regarding the usefulness of ultrasound.

4.10.2 | Q2. Does ultrasound lead to safer injections (not including ultrasounds as an adjunct in confirming the diagnosis of a VAE or in treating an established VAE)? ($n = 15$)

Among the participants, 53% ($n = 8$) did not believe that ultrasound leads to safer injections, while 47% ($n = 7$) expressed a belief in the safety benefits of ultrasound-guided injections.

4.10.3 | Q3. In what areas is ultrasound used? ($n = 12$)

The areas where ultrasound could be utilized effectively for injectables were identified, including the deep pyriform, temple region, nose, cheek, jawline, and tear trough regions. Three physicians (25%) recommended alternative applications for ultrasound in regions such as the glabella, lips, and intra-medial cheek.

4.10.4 | Q4. Do you feel ultrasound is the current standard for complication management? ($n = 15$)

Most [53% ($n = 8$)] of respondents disagreed with the statement that ultrasound is currently a standard for the management of complications, while 47% ($n = 7$) expressed agreement.

4.10.5 | Q5. Do you feel ultrasound will be the standard prior to filler injections within 10 years? ($n = 14$)

Among the participants, 57% ($n = 8$) of respondents disagreed, while 43% ($n = 6$) of respondents believed that ultrasound will become a standard procedure before filler injections within the next 10 years.

4.10.6 | Q6. Do you feel pretreatment ultrasound will be the standard for management of filler complication within 10 years? ($N = 13$)

Most respondents [69% ($n = 9$)] believed that pre-treatment ultrasound will become a standard for managing filler complications within the next 10 years, and 31% ($n = 4$) of respondents disagreed. Time will tell whether this will hold true.

5 | MOST RECENT ADVANCEMENTS IN THE TREATMENT AND MANAGEMENT OF VAE

Vascular occlusion in aesthetic procedures poses serious risks, primarily from filler injections into blood vessels. It can block blood flow, causing issues like ischemia and vasospasm. DeLorenzi's regional high-dose hyaluronidase protocol is an effective treatment introduced in 2017. An alternative method involves identifying affected skin areas, locating perforators with ultrasound, and administering hyaluronidase injections.[26] Frequent and repetitive hyaluronidase injections and follow-up assessments are vital. Products for managing reperfusion injury with steroids, oxygen therapy, and hyperbaric oxygen are lacking. Understanding the causes of VAEs, using hyaluronidase, and following protocols like the "Cutaneous Group Protocol" are key for safe aesthetic procedures.[27] Proactive reperfusion injury management enhances patient outcome.

5.1 | Vascular AE management: Survey and discussion

5.1.1 | Q1. Should the new protocol by the Cutaneous Group be adopted as the new standard? ($n = 14$)

The advisors were divided on whether the Cutaneous Group protocol should be adopted as the new standard,[27] with 54% ($n = 8$) of participants indicating their support for its adoption, and 46% ($n = 6$) of participants preferring to not adopt the new protocol as the new standard.

5.1.2 | Q2. In addition to hyaluronidase, are the following useful in treating VAEs? ($n = 12$)

- Nitroglycerin: 5 votes (42%)
- Aspirin: 10 votes (83%)
- Lidocaine: 1 vote (8%)
- Heparin: 2 votes (17%)
- Steroids: 6 votes (50%)

- Topical exosomes: 1 vote (8%)
- Hyperbaric oxygen (HBO) therapy or oxygen therapy: 10 votes (83%)

5.1.3 | Q3. In treating non-HA filler related VAE, is hyaluronidase used? ($n = 15$)

Among the panelists, 60% ($n = 9$) of respondents answered "Yes" when asked whether hyaluronidase is used, while 40% ($n = 6$) of respondents indicated "No." This suggests that a significant portion of the participants do employ hyaluronidase in the treatment of non-HA filler related VAE.

5.1.4 | Q4. Is ultrasound useful in the treatment of VAEs? ($n = 15$)

All 100% ($n = 15$) of participants agreed that ultrasound is useful in the treatment of VAEs.

5.1.5 | Q5. Can select VAEs be treated with observation, heat, massage, and aspirin (without hyaluronidase)? ($n = 15$)

The majority, comprising 67% ($n = 10$) of respondents, indicated that they did not consider these measures alone as sufficient for treating VAE in all situations and 33% ($n = 5$) of respondents indicated that they believe this approach can be effective in certain cases.

6 | SUMMARY OF SURVEY FINDINGS

- One important focus of the meeting was the development of a global AEs database. A global database for tracking AEs in aesthetic medicine is highly favored by the panelist, with 93% ($n = 14$) consensus among participants. Participants debated the scope of the database, with a majority favoring the inclusion of all marketed injectables. Concerns included data standardization and whether non-medical contributors should be included.

  Nonetheless, prospective registries are significant and offer several avenues for exploration:

  Incidence rates and timelines: Registries help determine AE incidence rates and establish real-world timelines from treatment to late-onset AE symptoms.

  Standards: Registries play a pivotal role in setting AE management standards. They provide guidance on recommended sessions for specific treatments, aiding standardized care.

  Recommendation assessment: Registries assess the relevance of existing recommendations, aligning guidelines with real-world patient outcomes.

  Engagement strategies: Strategies for engaging healthcare professionals, patients, and researchers are crucial, including user-friendly platforms for tracking AEs and encouraging participation.

  Future research: Data collected informs future research and potential AE prevention, treatment, and management improvements.

  The use of prospective registries in the evaluation and improvement of AEs is a promising area of research and healthcare practice. It has the potential to enhance patient safety, standardize treatment protocols, and guide future healthcare policies and recommendations.
- Aspiration as a safety technique was favored by 73% ($n = 11$) of participants. Opinions varied on the duration of aspiration, with preferences for 10, 7, and 2 s. Most agree on the need for aspiration when injecting near the periosteum or specific anatomic regions (e.g., pyriform aperature, temporal region), but differences of opinion were observed for injections into soft tissue.
- A subset [43% ($n = 6$)] of participants currently use ultrasound in conjunction with injections. Opinions differed on whether ultrasound will become a standard practice performed before filler injections within 10 years, as it has not yet reached a widespread applicability.
- Most practitioners use cannulas (93%, $n = 13$), 71% ($n = 10$) believe larger cannulas (25G or larger) are safer than needles. Different cannula sizes were preferred for various treatment areas. There was no consensus regarding the safety of larger needle sizes.
- Various treatments, including acetylsalicylic acid, nitroglycerin, and hyperbaric oxygen therapy, have been used in treating VAEs and might be useful. Opinions varied on the use of hyaluronidase in non-HA related VAEs.
- Most panelist agree that intraluminal injection of filler to be the primary cause of VAEs. Opinions differed on whether external compression of an artery causes VAEs, especially in the nasal tip.
- Skin condition and color, capillary refill, and pain were ranked as the best endpoints for measuring VAEs. Opinions were divided on the need for better ways to measure endpoints.
- DeLorenzi's high-dose protocol was considered the gold standard for VAE by 93% ($n = 13$) of participants.[21] Opinions varied on the wait time between doses of hyaluronidase. Most panelist reported that they do not perform a skin test prior to hyaluronidase injection. Opinions differed on whether the new protocol proposed by the Cutaneous Group should be adopted as the new standard.[27]

7 | FUTURE DIRECTIVES

Managing delayed complications was identified as a high-priority topic for the upcoming meeting. Notably, there were differing

opinions on the effectiveness of ultrasound in AE prevention and management. Additionally, discussions about VAE management and ultrasound sometimes overlapped, which is a factor worth considering when planning future medical communication projects.

The advisors acknowledged that certain topics remain contentious, even in the presence of existing literature, and they recommended concentrating efforts on areas where clear guidance can be offered. There are opportunities for conducting a comprehensive review of published information, encompassing both fundamental scientific research and clinical data. This approach would enhance the scientific validity of these discussions.

The research findings underscored AE management and hyaluronidase protocols as pivotal subjects, drawing substantial attention within our investigation. The consistent fourth place ranking of cannulas versus needles across surveys signifies sustained relevance in the surveyed community. Notably, ultrasound's priority varied among distinct groups, securing a third-place importance among meeting attendees but ranking seventh for remaining advisors, hinting at differing perspectives. Additionally, a consensus emerged among advisors regarding the lower priority of "other treatment options beyond enzymes," suggesting a collective view that this area might demand less immediate focus.

8 | CONCLUSIONS

This paper presents the key themes from the STF meeting. Advisors came together with a keen interest in establishing a comprehensive global database. They unanimously agreed that this database should encompass all product types while maintaining anonymity, localized by country/region. The meeting identified VAE management and hyaluronidase protocols as top priorities for further discussion. In exploring VAE treatment options, HBO or oxygen therapy and acetylsalicylic acid were highlighted beyond hyaluronidase. Consensus emerged on DeLorenzi's[21] high-dose protocol as the gold standard for VAEs, with agreement on a suitable 30-min interval between hyaluronidase doses. Some topics, such as "Other treatment options beyond enzymes" and "intraluminal versus extraluminal," were collectively regarded as lower priorities. While there was consensus on the usefulness of aspiration and cannulas for safer injections, opinions on the utility of ultrasound in AE management varied. Skin color and condition, alongside capillary refill, were considered effective treatment endpoints, though there was acknowledgment among ~64% of advisors for the need of better measurements. The next meeting will focus on exploring delayed complications associated with aesthetic injectables.

AUTHOR CONTRIBUTIONS

All listed authors have made substantial contributions to the design, data acquisition and interpretation of data, manuscript drafting and/or revising and approved the final version for publishing. Additionally, all authors agree to be accountable for all aspects of their participation in this work.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

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