Soft Tissue Fillers: Safety & Complications

Karol A Gutowski, MD, FACS

24th State-of-the-Art in Facial Aesthetics
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AxcelRx Pharmaceuticals - Advisory Board
Suneva Medical - Instructor

Will discuss off-label uses
Will use brand names for ease of understanding
Objectives for Safe Injections

- Learn techniques to minimize complications
- Identify serious complications
- Be able to manage complications
- Review regulatory issues
Injectable Tissue Filler Options

**Hyaluronic Acids**
- Juvederm
- Voluma
- Volbella
- Restylane
- Belotero

*Reversible*

**Animal Collagen**
- Zyderm
- Zyplasty
- Evolence

**Human Collagen**
- CosmoDerm
- CosmoPlast
- Fascian
- Autologen
- Cymetra
- LaViv

**Stimulators**
- PLLA (Sculptra)
- PMM (Bellafill)

**Fat**

**CaHA** (Radiesse)

**Silicone**
Aquamid Abscess

Acute swelling 3 years after Aquamid injection

Recurrent abscess
Factors in Unfavorable Outcomes

- Patient selection
- Undertreatment
- Anatomic site
- Product selection
- Technique
- Judgment (overfill/under correction)
- Patient expectations
- Tissue damage
<table>
<thead>
<tr>
<th>Volume Loss</th>
<th>Volume Descent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fillers</td>
<td>Facelift</td>
</tr>
</tbody>
</table>
Proper Dermal Injection

- Too Superficial
- Too Deep
- Correct Placement

Needle lifted
Blunt Injection Cannulas
Blunt Injection Cannulas

Safety and effectiveness of injection of calcium hydroxylapatite via blunt cannula compared to injection by needle for correction of nasolabial folds

Kenneth R Beer, MD
Esthetic, General & Surgical Dermatology, West Palm Beach, FL, USA

• 20 patients – split face (not enough for adverse events)
• Needle side had more pain, redness, swelling
• Cannula side had better correction at 19 days
Tear Trough & Lower Lids

- Inject on periosteum
- Expect edema & ecchymosis
- Under correct
  - Touch up in 2 weeks
- Prolonged edema
  - Treat early
  - Hyaluronidase
- May persist for years

Not for novice injectors
Beware the Nose

• Tissue compression, not intravascular injection may lead to necrosis
• Very small volume injections in tip
  – Multiple sessions
• Deep injections in midline
  – On top of bone or cartilage
• Extreme caution in past rhinoplasty or scars
• Done by injectors familiar with rhinoplasty
Impending Necrosis with HA Fillers

3 hours after injection
1 day after hyaluronidase
5 days after hyaluronidase
Impending Necrosis with HA Fillers

Presented after 7 days

After 1 month, NO hyaluronidase

Clinical Outcomes of Impending Nasal Skin Necrosis Related to Nose and Nasolabial Fold Augmentation with Hyaluronic Acid Fillers

Background: Although there are several case reports of facial skin ischemic necrosis caused by hyaluronic acid filler injections, no systematic study of the clinical outcomes of a series of cases with this complication has been reported.

Method: The authors report a study of 29 consecutive patients who developed impending nasal skin necrosis as a primary concern, after nose and/or nasolabial fold augmentation with hyaluronic acid fillers. The authors retrospectively
“No-Touch” Technique for Lip Enhancement

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May and New York, NY.

Background: The purpose of this study was to examine the anatomical principles of lip structure as they relate to individualized lip enhancement procedures and to describe a technique that does not violate lip mucosa during injection.

Methods: A retrospective analysis of patients undergoing lip enhancement procedures between 2001 and 2014 was performed. Preprocedural and postprocedural photographs were analyzed for lip subunit changes. A regenerative treatment algorithm targeting specific anatomical subunits of lip is described.
Blunt Cannula Lip Injection

“No-Touch” Technique for Lip Enhancement

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Methods: A retrospective analysis of patients undergoing lip enhancement procedures between 2001 and 2014 was performed. Preprocedural and postprocedural photographs were analyzed for lip subunit changes. A respective treatment algorithm targeting specific anatomical subunits of lip is described.
Complications
Immediate Complications

• Over or Under Correction
• Implant Visibility
  – Injection too superficial
    • HA blue discoloration
      – Massage, Hyaluronidase
    • Particulate fillers (CaHA, PMM) white bumps
      – Needle unroofing & evacuation

• Vascular Compromise
  – Glabella most common?
Glabellar Vascular Compromise

5 days after HA injection
Glabellar Vascular Compromise

12 days after HA injection
Glabellar Vascular Compromise

Healed
# Vascular Compromise

<table>
<thead>
<tr>
<th>Arterial Occlusion</th>
<th>Venous Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>Delayed, dull pain, dark discoloration</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Massage</td>
</tr>
<tr>
<td>Immediate or early, blanching, severe pain</td>
<td>Warm compresses</td>
</tr>
<tr>
<td>Stop injection, attempt aspiration</td>
<td>2% nitroglycerin paste*</td>
</tr>
<tr>
<td>Massage</td>
<td>Injection of hyaluronidase (if caused by hyaluronic acid product)</td>
</tr>
<tr>
<td>Warm compresses</td>
<td>Consider hyperbaric oxygen in cases of impending massive skin necrosis</td>
</tr>
<tr>
<td>2% nitroglycerin paste*</td>
<td>Antibiotic therapy (topical, parenteral, or both)</td>
</tr>
<tr>
<td>Injection of hyaluronidase (if caused by HA product)</td>
<td>in cases of skin breakdown</td>
</tr>
<tr>
<td>Antibiotic therapy (topical, parenteral, or both) in cases of skin breakdown</td>
<td>Conservative debridement</td>
</tr>
<tr>
<td>Conservative debridement</td>
<td>Frequent follow-up</td>
</tr>
<tr>
<td>Frequent follow-up</td>
<td>Informed consent</td>
</tr>
<tr>
<td>Prevention</td>
<td>Smallest possible needle</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Smallest possible volume injected</td>
</tr>
<tr>
<td>Smallest possible needle</td>
<td>Proper plane of injection</td>
</tr>
<tr>
<td>Smallest possible volume injected</td>
<td></td>
</tr>
</tbody>
</table>
Early Onset Complications

- Temporary nodules
- Persistent nodules
  - Non inflammatory
  - Inflammatory
    - Fluctuant vs nonfluctuant
    - Treat as infection
- Angioedema
Delayed Onset Complications

• Persistent nodules
  – Non inflammatory
  – Inflammatory
    • Fluctuant vs nonfluctuant
    • Treat as infection

• May develop into chronic problem
  – Abscess, tissue loss

• Persistent malar swelling
Case Example 1

42 year old female

• HA (Restylane) injection for acne scars
• 3 hours later - white patch over injection site
• What do you do?
Case Example 1

42 year old female

- HA (Restylane) injection for acne scars
- 3 hours later - white patch over injection site
- What do you do?
  - Nitropaste
  - Warm compressed
  - Hyaluronidase

Immediate blanching upon injection or delayed reticulated duskiness after injection can identify impending necrosis
Case Example 1

42 year old female

- HA (Restylane) injection for acne scars
- 3 hours later - white patch over injection site
- 4 days later - skin slough
- Now what?
Case Example 1

42 year old female

- HA (Restylane) injection for acne scars
- 3 hours later - white patch over injection site
- 4 days later - skin slough
- Conservative skin care
  + Hydroquinone

2 years later
Case Example 2

46 year old female

- Multiple HA* injections to lower eyelids over 3 years
- 1 month later developed periorbital swelling
- Allergy testing negative
- What now?

* Restylane & Juvederm
Case Example 2

46 year old female

- Multiple HA* injections to lower eyelids over 3 years
- 1 month later developed periorbital swelling
- Allergy testing negative
- What now? 15 units Hyaluronidase per lower lid

* Restylane & Juvederm

4 days later
After 5 years, fullness resolved 2 weeks after 60U hyaluronidase injected per side
HA Migration

• 3 patients with tear trough injections resulting in inferior migration years later
• Resolved with hyaluronidase
Case Example 2

Lessons Learned from *Infraorbital* Filler Injections

• Volume replacement is challenging
• Higher potential for complications
• Eyelid skin is unforgiving (produces lumps & bumps)
• Superficial injections produce persistent fullness
• Careful injection technique (small amounts deep)
• Variable longevity in this location
• *Unpredictable* edema
Case Example 3

67 year old female

• 1 vial (in 5cc) PLLA (Sculptra) injected
• Palpable nodules 10 months later
• What now?
Case Example 3

67 year old female

• 1 vial (in 5cc) PLLA (Sculptra) injected
• Palpable nodules 10 months later
• Steroid injection  → No Effect
Case Example 3

67 year old female

- 1 vial (in 5cc) PLLA (Sculptra) injected
- Palpable nodules 10 months later
- Steroid injection → No Effect → Excision

Birefringent foreign material with surrounding inflammation
Case Example 3

Lessons Learned from PLLA Injections

• Use higher dilution (8-10cc per vial)
• Dilute 3-5 days in advance
• Inject in deep plane
• Subperiosteal periorbital injection
• Frequent massage
Sculptra Nodules

- Inject saline
- 5-FU
- Kenalog
Case Example 4

64 year old female

• Multiple HA injections in NLF
• What is this?
Case Example 4

64 year old female

• Multiple HA injections in NLF
• What is this? **Tyndall Effect** (Blue discoloration)
Case Example 4

64 year old female
- Multiple HA injections in NLF
- How to treat?
Case Example 4

64 year old female

- Multiple HA injections in NLF
- How to treat? **15 units Hyaluronidase**
Case Example 4

Lessons Learned from HA Injections

• Superficial injections can be visible
• Small volume injections, evaluate & re-inject if needed
• Hyaluronidase
  – 10 to 30 units (4 to 7 days to effect)
  – Local skin reactions common
    • Amphadase (bovine - skin test)
    • Hylenex (r-human)
    • Vitrase (ovine - skin test)
Case Example 5

51 year old female
• Pain, redness & swelling 2 weeks after HA injection
• Firm without fluctuance
• Treatment?
Case Example 5

51 year old female

- Pain, redness & swelling 2 weeks after HA injection
- Firm without fluctuance
- Cellulitis, no abscess
  - Antibiotics x 6 weeks
  - Minocycline + clarithromycin
Lessons Learned from Infections after HA Injections

- Sterile skin prep before injection
  - Remove make up
- Culture fluctuant nodules before antibiotics
- Steroids not useful, prolong infection
- Consider atypical mycobacteria & biofilm if infection occurs weeks after injection
  - Multiple antibiotic therapies
  - Enzymatic removal of biofilms controversial
    - Biofilm dissolution → macrophage migration & antibiotic penetration
    - Bacterial spread
Granulomas vs Infections

• Resorbable fillers
  – Low incidence of long-lasting or late complications

• Partially or completely nonresorbable fillers
  – More anaerobic infections & granuloma reactions
  – Harder to treat

• Bacterial infection tissue swelling
  – Edema & cellular foreign-body response

• Micro particle filler swelling
  – Foreign body granuloma
Granulomas vs Infections

• Infection
  – Progress slowly
  – Anaerobic growth conditions
  – Symptoms 1 to 2 weeks after injection

• Granuloma
  – No detectable bacteria
  – May appear years after injection
  – Associated with microparticles fillers
Long Lasting Low Grade Infections

- Culture negative nodules
- Mistaken for foreign-body granulomas
- Bacteria in biofilm
- Cysts on US
Noninvasive therapeutic options

- Aspiration
  - Rarely works after a few months
- Excision
  - Scars & disfigurement
- Antibiotics
  - Effective only before biofilm develops
- Steroids
  - Temporary effect, rebound, skin atrophy & telangiectasias
- 5-Fluorouracil
  - Temporary effect & rebound
New Concepts on Filler Problems

Many problems assumed to be foreign body granulomas or allergic reactions on the basis of negative bacterial cultures are now thought to be due to biofilms

(Wiest, 2009)

Biofilms are almost impossible to culture using current standard culture technology and may be treated incorrectly with steroids injections, instead of 2 or 3 antibiotics

(Christensen, 2009)
Biofilms

- Aggregate of microorganisms adherent to each other or a surface
- Embedded in a self-produced matrix of extracellular polymeric substance
- Cells in a biofilm are physiologically distinct from planktonic cells
- Biofilm growth mode causes large shift in gene regulation
- Increased resistance to antibiotics & detergents
Biofilm Formation & Cycle

- Initial Attachment
- Irreversible Attachment
- Maturation I
- Maturation II
- Dispersion
Biofilm Infection Challenges

- Increased antibiotic resistance (1000x drug needed)
- Leucocytes trapped & made ineffective
- Chemical communication promotes bacterial cooperation
- Dormant (persister) cells have decreased metabolism
  - Difficult to culture
  - Resistant to antibiotics
- Clinical failure to recognize infections
- **RESULT:** Low-grade smoldering infection
  - Low host response
  - High antibiotic resistance
  - Low possibility of positive culture
Biofilm Detection

- Biofilm detection requires fluorescent DNA stains or other chemical reactions
- May need 4 to 6 weeks on specific agar plates
Bacteria in Gel

H&E Stain

Gram Stain

PNA Probe

PNA Probe

Bjarnsholt 2009
Fillers Susceptible to Biofilm Complications

**Combination Gels** (more likely)
- Collagen–PMMA suspensions (Artecoll)
- HA–PMMA suspensions (Dermalive, Dermadeep, Dermatech)
- Bioplastique (silicone in polyvinylpyrrolidone)
- Evolution (polyacrylamideco-DADMA)
- Bio-Alcamid (polyalkylmide)
- Outline (procollagen)

**Homogenous Products** (less likely)
- Radiesse
- Silicone
- Polyacrylamides
Biofilm 2 Week Window

- 2-week period after implant placement when bacterial contamination can occur and develop a biofilm
- Timeline documented in orthopedic implants & other solid foreign body implanted material
- Avoid needle injections over the implant during the 2 weeks
- Dental procedures, facial trauma, or facial infections can introduce bacteria and produce biofilm
Lump After Filler Injection

- Non painful
- Non inflammatory
  - Reassure if HA
  - Watch
  - Massage
    (Evaluate your technique & amount injected)

- Painful or Inflammatory
  - Immediate or Early Onset (< 1 year)
    - Oral Antibiotic: 2 - 6 weeks
    - If fluctuant: I&D + Cx*
    - Hyaluronidase (if HA filler)
    - No steroid injections

  - Late Onset (> 1 year)
    - Particulate Filler
    - Assume Biofilm Activation
    - Multiple antibiotic: > 6 weeks
    - I&D + Cx*
    - Consider steroid injection (on Abx)
    - Excise or debride if possible
Antibiotic Treatment

Most Early Infections
• Clarithromycin 500 mg BID x 6 weeks
• Minocycline 100mg BID x 6 weeks

Recurrent infections suggest active biofilm
• Filler & biofilm must be removed/excised
Laser Treatment of Filler Lesions

- **Infectious lesions**
  - 532 nm lithium triborate laser
  - Removal of infected gel & pus
- **Granulomas**
  - 808 nm diode laser (intraleisional technique)
  - Melt & liquefied then granuloma
  - Facilitates evacuation
- **Thin laser beam**
  - Controlled tissue
- **20 patients had reduction or complete resolution**
  - Resolution increased with repeated treatments
  - All had prior antibiotics & steroids without success

*Cassuto 2009*
Laser Treatment of Filler Lesions

- Cystic lumps 3 months after HA & dextranomer microsphere injections
- 6 weeks antibiotics & steroids no resolution
- Multiple 532 nm lithium triborate laser treatments

Cassuto 2009
Laser Treatment of Filler Lesions

- Granulomas after Dermalive* & Aquamid**
- 808 nm diode laser treatment
- Drill holes for evacuation

* HA + acrylic hydrogel
** Polyacrylamide
Unintentional Injection of Soft Tissue Filler into Blood Vessels in the Face: FDA Safety Communication
Signs & Symptoms of Intraarterial Injection

• Skin
  – Pain
  – Skin blanching
  – Slow capillary refill
  – Demarcation

• Eye
  – Vision loss/blindness

• Stroke
  – “FAST”: facial drooping, arm weakness, speech impediment, time (act fast!)
## Progression of Skin Changes

<table>
<thead>
<tr>
<th>Findings</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanching</td>
<td>Seconds</td>
</tr>
<tr>
<td>Reactive hyperemia or livedo pattern</td>
<td>Minutes up to 10 minutes</td>
</tr>
<tr>
<td>Blue-black discoloration</td>
<td>10 minutes to hours</td>
</tr>
<tr>
<td>Blister/bullae formation</td>
<td>Hours to days</td>
</tr>
<tr>
<td>Skin breakdown, ulceration, slough</td>
<td>Days to weeks</td>
</tr>
</tbody>
</table>

Low Volume Injection & Arterial Occlusion

High Injection Pressure & Retrograde Propagation

Avoid Arterial Injection & Propagation

- Withdraw before injection
- Avoid deep injection near named vessels
- Low pressure injection
- Avoiding injecting excess volume in one area
- Blunt cannulas
- Small bore
- Inject slowly in small aliquots
- Avoid injection in previously traumatized areas
- Stop injection if complaints of pain/vision loss

Blindness

Crash Kit

- Warm compress
- Nitropaste
- Baby ASA
- Supplemental O2
- **HYALURONIDASE**
  - 400u into subcutaneous area (2cc in a 3cc syringe with 0.2cc plain lidocaine 2%, 27 g-needle)
Transarterial Degradation of Hyaluronic Acid Filler by Hyaluronidase

Claudio DeLorenzi, BA, MD, FRCS

Intravascular HA liquefied in cadaver arteries & veins after 4 hours
Hyaluronidase works for
Juvederm
  Ultra & Ultra Plus
  Voluma & Volbella
Restylane
  Lyft & Silk
Belotero

Always have Hyaluronidase available when doing HA injections
Filler Emergencies

• Soft tissue intravascular occlusion
• Stroke
  – Standard emergency stroke protocol
• Vision loss/blindness
  – Emergency ophthalmology consult
  – Retrobulbar hyluronidase injection
Retrobulbar Injection Technique

• Local anesthesia into lower eyelid over inferotemporal orbit
• Blunt, 25g cannula advanced in inferotemporal quadrant of orbit for 1 inch
  – Inferior and lateral to optic nerve
• 2 to 4cc hyaluronidase
Retrobulbar Injection Technique
What Next?

- Wound care
- See patient daily
- Consider Hyperbaric Oxygen
Complications
Use Informed Consent Forms!
Filler Complications

• All fillers have potential complications
• Long lasting
  – More persistent
  – More difficult to treat
• Complications due to technique vs material
  – Learn technique on temporary fillers
  – Experience decreases technique complications
• Train ALL STAFF on filler emergency calls
  – Text a picture of any “bruising”
Recommendations

• Know the filler material you are using
• Start with temporary & reversible products
  – Hyaluronic acids
• Use sterile techniques
• Limit amount injected & areas treated
  – Easier to add than to take away
• Deal with inflammatory nodules
• Know the regulatory issues
Regulatory Issues
Fillers & the Law

- Product purchase source
- Non-FDA approved fillers
- Patient supplied fillers
- Off label filler use
- Reimporting FDA approved fillers
- Physician vs non-physician filler injector
- Non-clinical treatment settings
5 Docs Plead Guilty in Bogus Botox Rap; Stems From Toxin Research International Case

By Jim Edwards | Aug 14, 2009

Five prominent New York State doctors pled guilty this week to injecting patients with an unapproved version of Botox, and not telling those patients they weren’t getting the real thing. They face a possible year in prison and a $100,000 fine on a misdemeanor misbranded drugs charge.

The doctors bought the Botox from Toxin Research International in Arizona. The doctors maintain they thought it was the real thing, and no patients were injured.

The president of Toxin Research International is currently serving nine years in prison for fraudulently selling misbranded Botox on the web.

The case is a warning to doctors: get your supplies through established channels, not the secondary market.

These weren’t sleazy docs operating out of strip malls. Their resumes read like pillars of the community.
Is it legal for a physician to obtain and use a product from outside of the United States that is not approved by the FDA?

- An individual who enters the country with a non-approved injectable filler could be sanctioned by the FDA
- A physician who orders a non-approved injectable filler through a non-US mail-order pharmacy could be sanctioned by the FDA
- State medical board involvement if any patient complaints result
- Exceptions for investigators working under FDA-approved studies
Patient Provided Fillers

If a patient brings a non-approved drug or device to a physician, is it legal to treat the patient using this drug or device?

- Federal law prohibits such conduct
- Risk of significant liability exposure, invalidation of professional liability insurance coverage, criminal penalties and action by regulatory agencies
What is the risk exposure of off-label use of approved drugs?

- Off-label use of FDA approved drugs does **not** carry the risks cited above, provided patient acceptance and understanding, and the treatment rationale, are well documented.
- For example, Botulinum toxin type A is a FDA-approved product for use in the glabellar area. Use of the product in other areas is legal and a clinical decision.

Can a physician advertise non-approved or off-label use?

- It is illegal to commercially advertise any non-approved or off-label use; only FDA-approved uses may be commercially advertised.
Reimported Fillers

Is it legal for a physician to purchase and use an FDA approved drug/product that is reimported from foreign sources?

- The act of importing drugs manufactured or approved in the U.S. and approved by the FDA is called “reimportation”...which remains illegal and dangerous
- Currently, only manufacturers are allowed to reimport their own drugs
Non-Physician Filler Administration

What level of training or licensure is required to administer injectables or fillers?

• Injections may be administered by a licensed professional nurse or physician assistant as determined by the supervising physician & local and state professional practice regulations
• Physician’s responsibility to ensure the non-physician possess proper education and training

What are the legal requirements for physician supervision of non-physician personnel who administer injectables and fillers?

• Supervisory regulations vary from state to state
• Physician of record is ultimately responsible
Non-Clinical Treatment Settings

• Administration of injectables & fillers outside a clinical setting
• Concern about non-clinical sites where treatments offered
  – Shopping malls, private homes, office parties, and group social gatherings
• Inappropriate for several reasons:
  – Inadequate patient selection
  – Possible peer pressure for an individual to consent to treatment
  – Providers who are not trained or qualified to treat or deal with complications
  – Lack of control over dosage and inadequate post-treatment supervision
  – Alcohol influencing decision making
  – Dealing with adverse event

Update In Process
Soft Tissue Fillers: Safety & Complications

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