Bulking Agents for Stress Urinary Incontinence

Dr. J. Matthew Andrews B.Sc, M.Sc, MD, FRCSC
Clinical Assistant Professor
Memorial University
Disclosures

• Lecturer
  • Astellas Pharma Canada
  • Pfizer

• Advisor
  • Sanofi
Armamentarium against SUI

Non-Surgical
• Observation
• Continence Pessary
• Vaginal Inserts
• Pelvic Floor Muscle Exercises

Surgical
• **Bulking Agents**
• Midurethral sling (synthetic)
• Autologous Fascia Pubovaginal Sling
• Burch colposuspension
• Artificial Urinary Sphincter
In index patients considering surgery for stress urinary incontinence, physicians may offer the following options: (Strong Recommendation; Evidence Level: Grade A)

- Midurethral sling (synthetic)
- Autologous fascia pubovaginal sling
- Burch colposuspension
- Bulking agents

AUA / SUFU Guideline 2017

• In patients with stress urinary incontinence and a fixed, immobile urethra (often referred to as ‘intrinsic sphincter deficiency’) who wish to undergo treatment, physicians should offer: (Expert Opinion)
  • Pubovaginal slings
  • Retropubic midurethral slings
  • Urethral bulking agents
Bulking agents – Patient Selection

• First described as early as 1904
  • Injection of periurethral paraffin wax for SUI

• Viable option for SUI in select patient population

• Alternative option for:
  • Salvage procedures post-failure of MUS
  • Patients with contraindication to MUS

Table 1. Indications for periurethral bulking for female stress urinary incontinence (SUI)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient choice</td>
<td>• Low to moderate volume SUI</td>
</tr>
<tr>
<td></td>
<td>• Accepts lower likelihood of success versus surgery</td>
</tr>
<tr>
<td>Young patient who desires future pregnancy</td>
<td>As above</td>
</tr>
<tr>
<td>Poor bladder emptying</td>
<td>Lower risk of permanent urinary retention vs. surgery</td>
</tr>
<tr>
<td>Poor candidate for surgical intervention</td>
<td>• High anesthetic risk</td>
</tr>
<tr>
<td></td>
<td>• Stenotic introitus</td>
</tr>
<tr>
<td></td>
<td>• Advanced age</td>
</tr>
<tr>
<td></td>
<td>• Severe obesity</td>
</tr>
<tr>
<td></td>
<td>• Anticoagulated</td>
</tr>
</tbody>
</table>
Mechanism of action

- Augment or restore mucosal coaptation without obstructing urination
- Injected into the submucosal space to elevate the urethral mucosa
  - increases coaptation and urethral resistance
- Inject at bladder neck or proximal urethra

1 Mamut & Carlson CUAJ 2017
Technique Aspects

- Outpatient setting
- Anesthesia: **Local** vs IV sedation vs general
- Peri-urethral or trans-urethral injections
- Cystoscope with 0 degree lens
- 23-gauge 120mm needle
- 3 - 4 equally spaced submucosal injections at level of proximal urethra and/or bladder neck
- Minimize passage of scope across bladder neck
- Drain bladder with small in/out catheter
- Repeat injections in 1-3 mths if incontinence persists
Ideal Bulking Agent

• Easy to inject
• Non-immunogenic, non-carcinogenic,
• Biocompatible
• Non-migratory
• Cost-effective
• Non-inflammatory
• Sufficient durable clinical improvement

<table>
<thead>
<tr>
<th>Available agents</th>
<th>Bulking agent</th>
<th>Material</th>
<th>Particle size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-linked collagen</td>
<td>Contigen®</td>
<td>Bovine collagen</td>
<td>N/a</td>
</tr>
<tr>
<td>Permacol®</td>
<td>Collagen piglet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Particulate combination Gels (Mini-particles suspended in a carrier gel)</td>
<td>Zuidex®</td>
<td>Dextranomer hyaluronic acid</td>
<td>80 - 200</td>
</tr>
<tr>
<td>Deflux®</td>
<td>Dextranomer hyaluronic acid</td>
<td>80 - 250</td>
<td></td>
</tr>
<tr>
<td>Macroplastic®</td>
<td>Polydimethylsiloxane</td>
<td>73 – 100</td>
<td></td>
</tr>
<tr>
<td>Durasphere EXP®</td>
<td>Carbon coated beads</td>
<td>90 – 212</td>
<td></td>
</tr>
<tr>
<td>Opsys®</td>
<td>Polycrystalline polyalcohol copolymer</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Coaptite®</td>
<td>Calcium hydroxylapatite</td>
<td>75 - 125</td>
<td></td>
</tr>
<tr>
<td>Silicon elastomer</td>
<td>Uryx / Tegress®</td>
<td>Vinyl alcohol copolymer implants</td>
<td>N/a</td>
</tr>
<tr>
<td>Urolastic®</td>
<td>Crosslinked vinyl dimethyl polydimethylsiloxane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homogenous hydrogel</td>
<td>Bulkamid®</td>
<td>Hydrogel Polyacrylamide (PAHG) 97.5% water and water 2.5% cross-linked polyacrylamide</td>
<td>N/a</td>
</tr>
</tbody>
</table>

Withdrawn from market for safety or commercial reasons

Courtesy Dr. G. Nadeau
Efficacy

- Clinical data on bulking agents is limited and heterogenous
- Majority of literature focuses on subjective improvement rather than objective improvement measures
- Long term follow-up is lacking
- Cochrane review 2017\(^1\)
  - 14 trials – small, moderate quality
  - Insufficient data to allow for meta-analysis or clinical decision making
  - Select agents shown to be more effective than pelvic floor muscle therapy, but less effective than open surgical management for SUI
- Overall, efficacy ranges 50-70% for early subjective improvement\(^2\)
  - Not sustainable and lacks durability over time
- Inadequate data to recommend one injectable agent over another

\(^1\) Kirchin V et al. Cochrane Database of Systematic Reviews 2017, Issue 7.
\(^2\) Kocjancic et al. Neurourol Urodyn. 2019
Hyaluronic acid and Dextranomer microspheres

• Viscous gel
• Biocompatible
• **Zuidex®** (Periurethral injection) – **removed from market**
  • High complication rate
  • Lower success rates compared to Collagen (53% vs 66.5%)

• **Deflux®** (Transurethral injection)
  • Lightner et al. Urol 2010
    • 4/35 pts developed pseudoabscess requiring operative management
    • Failed for 23/35 pts with ISD

\(^1\)Lightner et. al. Urol 2009
Polyarcylamide hydrogel (PAHG) - Bulkamid®

- Injectable hydrogel consisting of 97.5% water and 2.5% cross-linked polyacrylamide
- Homogeneous (no micro-particles)
- Non-degradable and non-migratory
  - Exchanges water, salts and organic molecules with host tissue
- Pivotal study
  - 345 women with SUI, randomized 2:1
  - PAHG non-inferior to collagen
  - At 12 mths, 53% improved, 47% cured
  - 77% required repeat injections

1 Sokol et al. JUrol 2014
Safety

• ~ 1/3 of patients experience some complication\textsuperscript{1}
  • Majority low grade, transient, noninvasive tx (ie. ABX, catheter)

• Potential adverse events\textsuperscript{2}
  • \textit{Urinary tract infection}
  • \textit{Injection site pain}
  • Urinary retention
  • Hematuria
  • Periurethral abscess
  • De novo urgency urinary incontinence
  • Bulking agent extrusion
  • Delayed hypersensitivity reaction
  • Granuloma formation

\textsuperscript{1} Kocjancic et al. Neurourol Urodyn May 2019
\textsuperscript{2} Mamut & Carlson CUAJ 2017
Contraindications

• Hypersensitivity to the agent
• Active urinary tract infection
Patient Counselling

- Minimally invasive
- Low tx morbidity
- Improved coaptation

- Efficacy & durability inferior to surgical slings for SUI
- Repeat injections may be required

Summary

• Viable option for select patients
  • Non candidates for more invasive surgical interventions
  • Multiple prior failed surgeries
• Efficacy is modest at best
• Not as effective as slings
• Repeat injections are the norm