

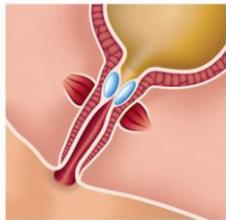
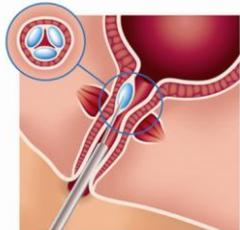
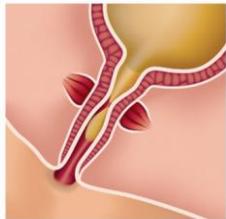
Bulking Agents

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Assaf Harofeh Medical Center



+ Periurethral Bulking Agents



What is urethral injection therapy?

“The injection of bulking agents into the urethral submucosa is designed to create artificial urethral cushions that can improve urethral coaptation and hence restore continence”.

Cochrane Review - 2003

+ History



- Paraffin *(Meyer - 1904)*
- Sodium murrhate *(Murless - 1938)*
- Polytetrafluoroethylene (Teflon®) *(Politano/Berg - 1973)*
- Bovine collagen (Contigen®) *(Knopp - 1977)*
- Autologous fat *(Shortliffe/Garibay - 1989)*
- Silicon particles (Marcoplastique®) *(Bucklay - 1992)*
- Dextranomer/hyaluronic acid (Zuidex®/Deflux®) *(Stenberg - 1999)*
- Carbon coated beads (Durasphere®) *(Lightner – 1999)*
- Calcium hydroxylapatite (Coaptite®) *(Mayer 2001)*
- Etylene vinyl alcohol (Tegress®) *(Karram – 2003)*
- Polyacrylamide hydrogel (Bulkamid®) *(Lose – 2006)*



+ Mechanism of action



- Mucosal coaptation → ↑ Urethral closure pressure
↑ Resistance to the passive outflow of urine

Winters JC & Appell R, Urol Clin North Am, 1995

- Cephalad elongation of functional urethral length → ↑ pressure transmission to proximal $\frac{1}{4}$ of urethra → resisting bladder neck opening during stress

Monga AK & Stanton SL, Br J Obstet Gynaecol, 1997

- ↑ stretch of muscle fiber → ↑ rhabdomyosphincter contractility

Klarskov N & Lose G, Neurourol Urodyn, 2008



+ Ideal Bulking Agent



- Material safety: non-antigenic, non-infectious, and non-carcinogenic
- Anatomic integrity: - Conserving volume over time
- Lack of distant migration (particle size $>110 \mu\text{m}$)
- No special preparation or handling before injection
- Adequate viscosity and easy injection
- Incorporation into the body with excellent healing
(minimal fibrosis and inflammatory response)
- The volume after injection should be retained with minimal resorption



+ Indications for Bulking Agents



- Classical indication: patients with poor urethral function and limited urethral mobility.
- More recently, several trials suggested efficacy in treating SUI due to urethral hypermobility as well.

Steele et al. *Obstet Gynecol* 2000

Herschorn S, Radomski SB. *Int Urogynecol J Pelvic Floor Dysfunct* 1997

The ideal candidate:

- good anatomical support
- a compliant, stable bladder
- a malfunctioning urethra, evidenced by a low LPP.



+ Indications for Bulking Agents



Unique clinical situations:

- frail or elderly population
- treatment of secondary incontinence in women who have undergone multiple failed procedures
- after radiotherapy and/or radical hysterectomy, where the urethra is fixed and scarred

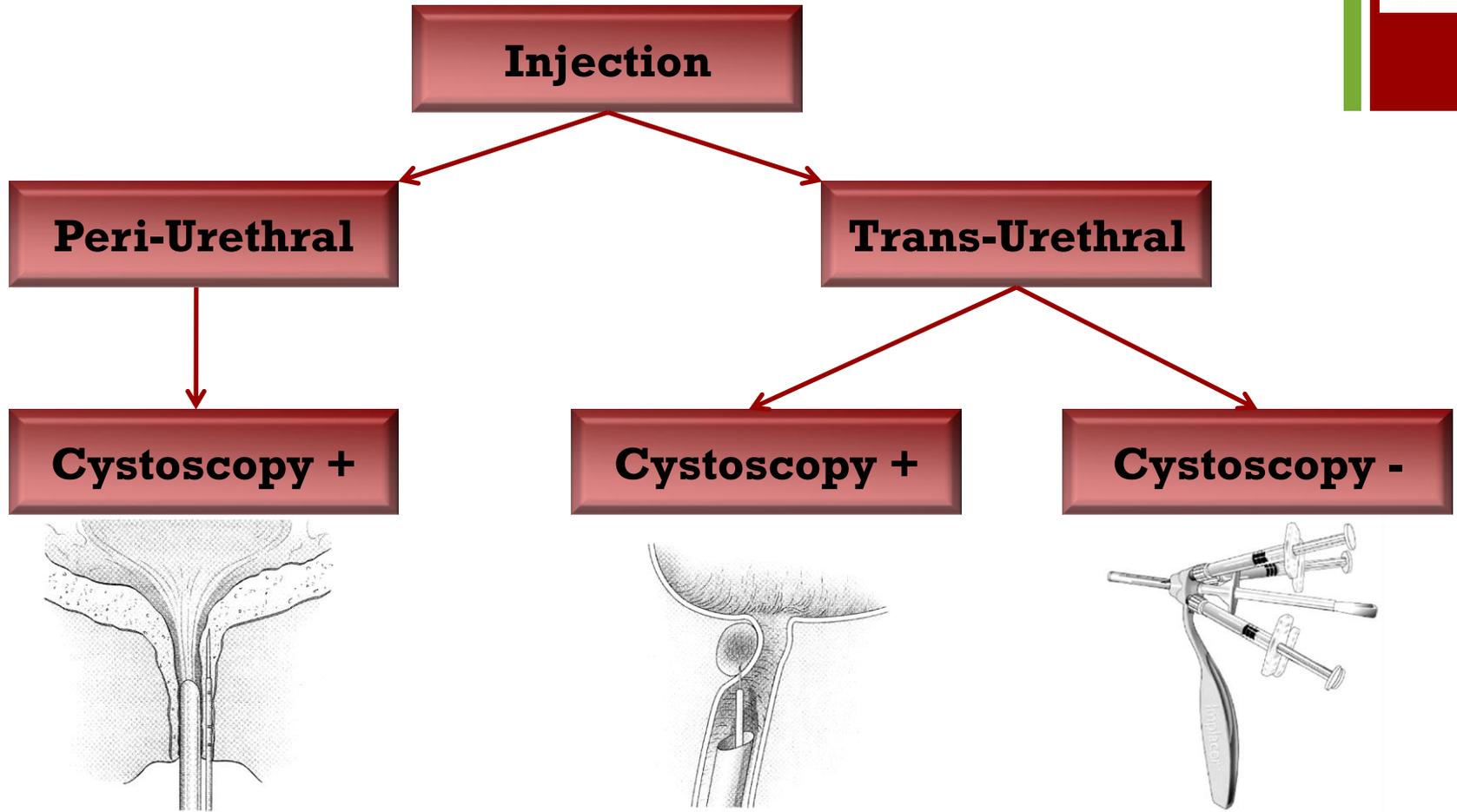
Krhut J et al, . *Int Urogynecol J Pelvic Floor Dysfunct* 2015
Plotti F et al., *Gynecologic Oncology* 2009

- SUI after genito-urinary fistula surgery

Krause HG et al, *J. Obstet. Gynaecol. Res.* 2014



+ Mode of Administration



Bladder neck or midurethral injection?



+ Types of Bulking Agents



Combination gels – mini-particles in transient carrier gel

Structural - the bulking derives from host inflammatory response to mini-particles

Homogenous gels – polymers

Volumetric - the bulking derives from the gel itself



+ Clinical Outcome



	Contigen®	Durasphere®	Tegress®	Macroplastique®	Coaptite®	Zuidex/D eflux®	Bulkamid®
Volume	Up to 15 cc	3 cc	2.5 cc	5 cc	1.9-5.5cc	2.8 cc	1.5
1-year improvement rate	62% (40-60%)	65%-80%	59-74%	75%	63%	76%	66-79%
Long term outcome	30-40%	20-30%		48-58%		57%	64%
Repeated injections	33%-75%		75%		62%	43%	24.3%
Difficult injection		+	+				

Starkman JS et al, Current Urology Reports 2006
 Appel RS, BJU 2006
 Kirchin_et_al-2012-The_Cochrane_Library



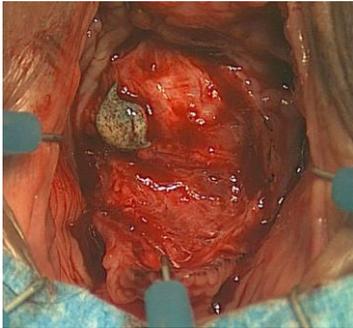
+ Complications



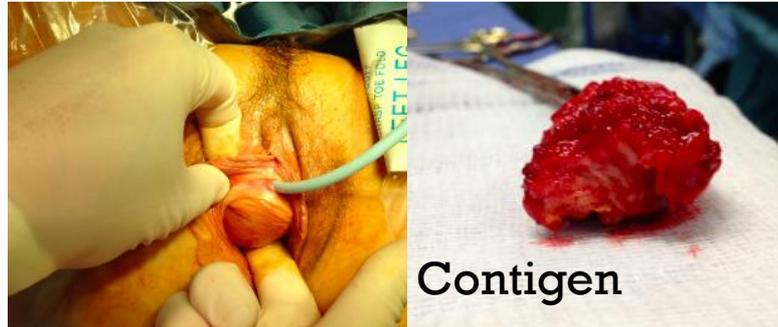
	COLLAGEN Contigen®	CARBON-COATED BEADS Durasphere®	CALCIUM HYDROXY-PATITE Coaptite®	EVHO Oryx® Tegress®	SILICONE ELASTOMER Macroplastique®	DEXTRANOMER /HYALURONIC ACID Zuidex/Deflux®	POLYACRYLAMID HYDROGEL Bulkamid®
Migration	No	Yes		No	Yes	No	No
Granuloma		3%	Yes		(Yes)	Yes	No
Sterile Abscess (Pseudocyst)	Yes	Yes				17%	No
Erosion		Yes	Yes	16%		Yes	
Calcification	Yes				Yes		
Allergy	4%						
Urethral prolapse	Yes	Yes					



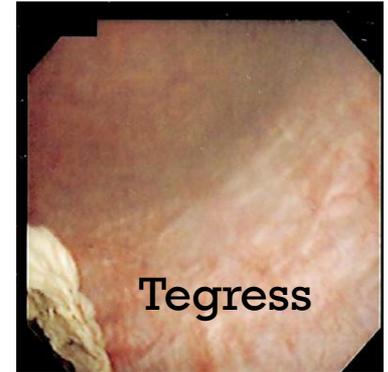
+ Complications of bulking agents



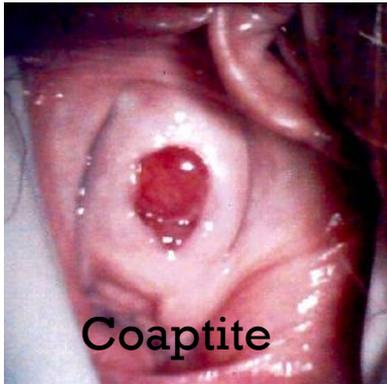
Durasphere



Contigen



Tegress



Coaptite



Zuidex





The evidence for Bulking Agents Use



THE COCHRANE
COLLABORATION®

Urethral injection therapy for urinary incontinence in women (Review)

Kirchin V, Page T, Keegan PE, Atiemo K, Cody JD, McClinton S

2012

Authors' conclusions

The available evidence base remains insufficient to guide practice. In addition, the finding that placebo saline injection was followed by a similar symptomatic improvement to bulking agent injection raises questions about the mechanism of any beneficial effects. One small trial comparing silicone particles with pelvic floor muscle training was suggestive of benefit at three months but it is not known if this was sustained, and the treatment was associated with high levels of postoperative retention and dysuria. Greater symptomatic improvement was observed with surgical treatments, though the advantages need to be set against likely higher risks. No clear-cut conclusions could be drawn from trials comparing alternative agents, although dextranomer hyaluronic acid was associated with more local side effects and is no longer commercially available for this indication. There is insufficient evidence to show superiority of mid-urethral or bladder neck injection. The single trial of autologous fat provides a reminder that periurethral injections can occasionally cause serious side effects.



+ Current Usage status



■ Bulking Agents on the market today:

- Bulkamid®
- Deflux®
- Durasphere®
- Macroplastique®



Meta-analysis on complications (Abstract, ICS 2015)



A META-ANALYSIS OF COMPLICATIONS ASSOCIATED WITH URETHRAL BULKING AGENTS IN THE TREATMENT OF STRESS URINARY INCONTINENCE

Dobbs R1, Islam M2, Wadhwa H1, Malhotra N1, Kocjancic E1

Study design, materials and methods

A meta-analysis of the scientific literature from 1996 to 2014 was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. 4,326 patients from 78 studies/study samples were analyzed and were eligible for inclusion. Complications of injections were analyzed and incidence was recorded, along with complication treatment incidence and efficacy

Results

1,999 complications were reported. 3.8% were considered serious. Of these, 70.6% required incision and drainage and 29.3% required a more invasive procedure. Major complication rates for all complications were: **dextranomer/hyaluronic acid (17.8%), carbon coated zirconium (11.4%), ethylene vinyl alcohol copolymer (10%), calcium hydroxylapatite (8.7%), collagen (1.8%), polyacrylamide hydrogel (0.8%) and polydimethylsiloxane (no serious complications reported)**

Concluding message

For currently commercially available UBAs, polydimethylsiloxane and polyacrylamide hydrogel appear to have the most favorable safety profiles in regards to major complications.



+ Durability of bulking effect (Poster, ICS 2015)



Long-term effectiveness and durability of Bulkamid® as primary treatment of stress urinary incontinence – a longitudinal study

*Lobodasch K, Brosche T
Frauenklinik DRK-Krankenhaus Chemnitz, Germany*

- Longitudinal study on 352 women (255 SUI and 97 MUI)
- Ave age 67 (29-95); BMI 30 (17-64); Parity 1.9 (0-8)
- Mean use of pads reduced from 4.1 to 1.76 postoperatively

Cured: negative stress test and $\geq 90\%$ VAS improvement
Improved: losing only a few drops during stress test and $\geq 60\%$ VAS improvement
Failed: urine loss during stress test and $\leq 50\%$ VAS

Fig. 3. Bulkamid® subjective efficacy at the latest follow up

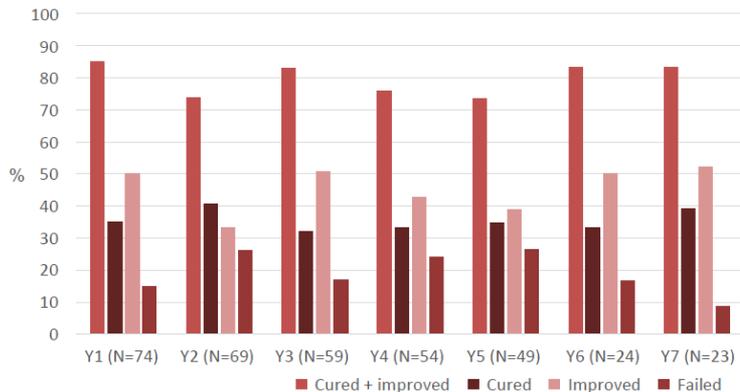
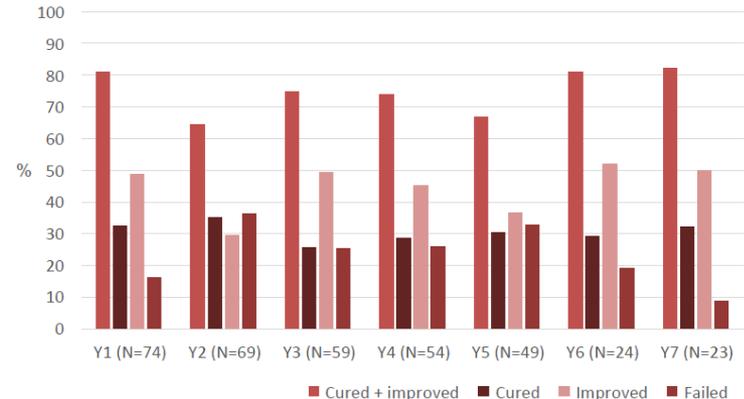


Fig. 4. Bulkamid® objective efficacy at the latest follow up





Urethral Bulking for Recurrent Stress Urinary Incontinence after Midurethral Sling Failure

Spital Thurgau
FRAUENFELD

Coombe Women & Infants University Hospital
Cúisceal Oifigeallaíon agus Níobairín an Chláin
Partners in the Care of Women and Babies
Hospital Group for Women

Deutsches
Rotes
Kreuz

Zivanovic I¹, Rautenberg O¹, Lobodasch K², Crosby DA³,
Von Büнау G³, Walser C¹, Viereck V¹

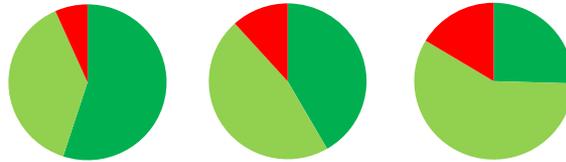
¹ Department of Gynaecology and Obstetrics, Cantonal Hospital, Frauenfeld, Switzerland

² Department of Gynaecology, German Red Cross Hospital Chemnitz-Rabenstein, Chemnitz, Germany

³ Coombe Women and Infants University Hospital, Dublin, Ireland



■ cured
■ improved
■ failed



Outcome	≤1 month (n=60)	6 months (n=60)	12 months (n=55)
cured	33 (55%)	25 (42%)	14 (25%)
improved	23 (38%)	28 (47%)	32 (58%)
failed	4 (6.7%)	7 (12%)	9 (16%)

Complications	≤1 month (n=60)	6 months (n=60)	12 months (n=55)
persistent urgency	12 (20%)	10 (17%)	11 (20%)
voiding dysfunction, RU≥100ml	8 (13%)	5 (8.3%)	1 (1.8%)
UTI postop	3 (5.0%)	7 (12%)	2 (3.6%)
de novo urgency	1 (1.7%)	2 (3.3%)	2 (3.6%)

- **Prospective study conducted to assess the efficacy and safety of Bulkamid® in treating recurrent SUI after MUS failure**
- 60 patients with MUS failure; 32% of patients had mixed urinary incontinence (MUI) prior to surgery
- Mean 1.84 ± 0.4 ml Bulkamid® was injected
- Cure rates were assessed objectively and subjectively

Post-operative complications:

- No cases of urge incontinence
- Haematuria, injection site laceration and hematoma rates were < 2%
- No injection site pain or urinary retention

Zivanovic et al, IUGA 2015



+ MUS following bulking agents



Safety and Efficacy of Sling for Persistent Stress Urinary Incontinence After Bulking Injection

Michelle E. Koski, Ekene A. Enemchukwu, Priya Padmanabhan, Melissa R. Kaufman, Harriette M. Scarpero, and Roger R. Dmochowski

Table 4. Outcomes with follow-up

Length of follow-up, y (No. of Patients)	1-2 y (17 patients) n (%)	2-3 y (7 patients) n (%)	3-4 y (5 patients) n (%)	4-5 y (7 patients) n (%)	> 5 y (7 patients) n (%)
Subjective outcome					
Cured/no leak	10 (58.8%)	3 (42.9%)	4 (80.0%)	5 (71.4%)	4 (57.1%)
Improved	6 (35.2%)	4 (57.1%)	1 (20.0%)	2 (28.6%)	2 (28.6%)
Same	1 (5.9%)	0	0	0	0
Insufficient data	0	0	0	0	1 (14.3%)



Koski ME, *Urology* 2011



Thank you for your continence!

