Minimally Invasive Therapies for SUI
Mini Slings &Bulking Agents

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Gibraltar


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S
PORTUGAL
SPAIN
Mediterranean Sea
Strait of Gibraltar
Gibraltar (U.K.)
Ceuta (Spain)
Melilla (Spain)
ATLANTIC OCEAN
MOROCCO
ALGERIA
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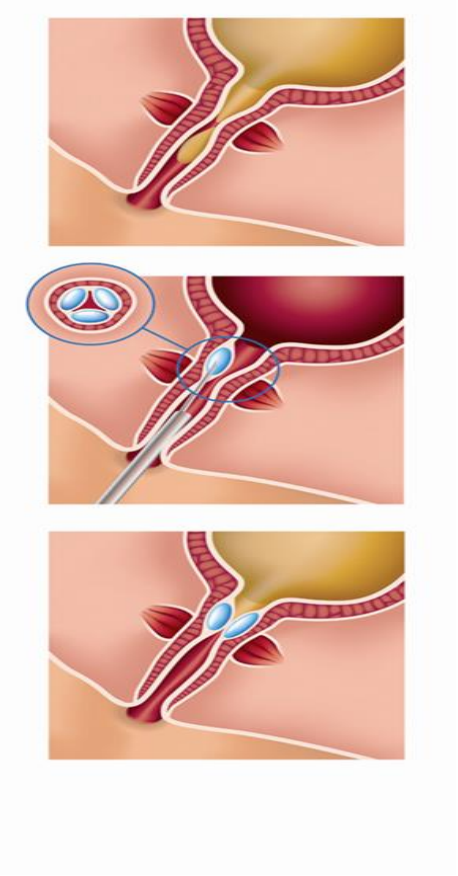
What is Bulking Agents

"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



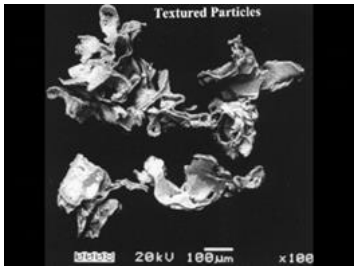
History of Bulking Agents

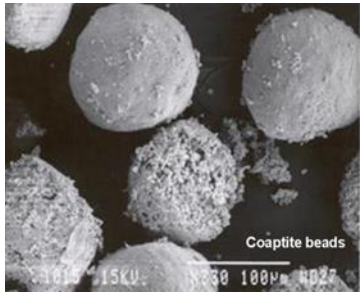
- Paraffin (Meyer - 1904)
- Sodium murrhate (Murless - 1938)
- Polytetrafluoroethylene (Teflon®) (Politano/Berg - 1973)
- Bovine collagen (Contigen®) (Knopp - 1977)
- Autologous fat (Shortliffe/Garibay - 1989)
- Silicon particles (Marcoplastique®) (Bucklay - 1992)
- Dextranomer/hyaluronic acid (Zuidex®/Deflux®)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

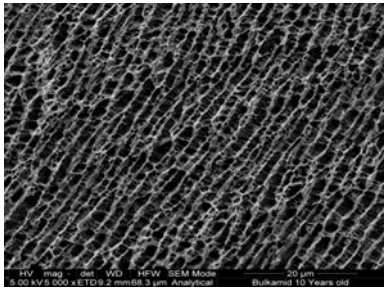
Characteristics for the Ideal Bulking Agent

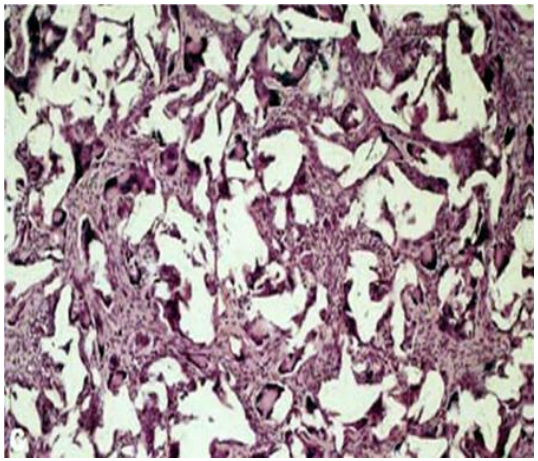
- Biocompatibility
- No immunogenicity
- Integrity of the material formulation
- Adequate viscosity
- Minimal fibrosis
- Little inflammatory response
- Volume should be retained after injection
- No re-injections needed over time
- Total incorporation in the tissue

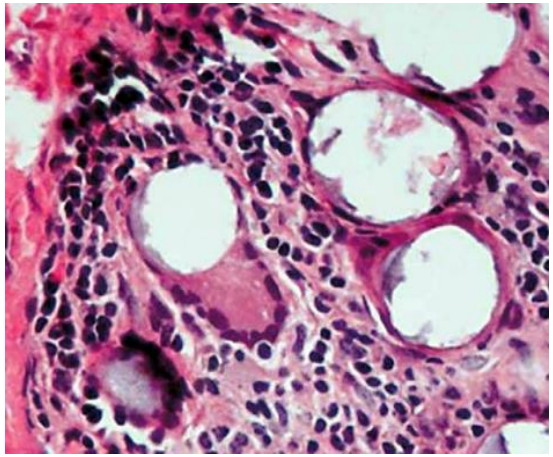
Structure and Tissue Interaction of some Bulking Agents

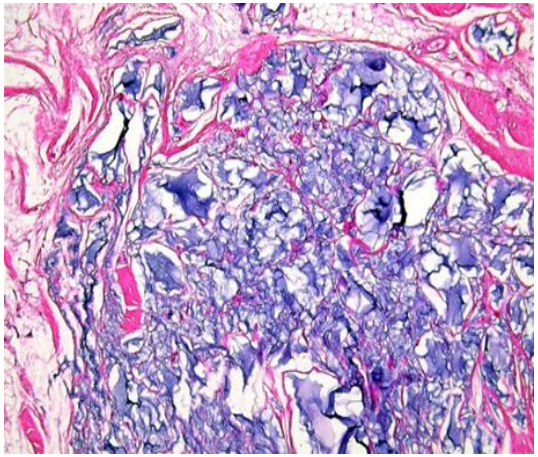












MACROPLASTIQUE

COAPTITE

BULKAMID

Two different 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

Differences between bulking agents

Combination agents	Homogeneous - Bulkamid
• Risk of migration of micro particles	• No migration
• Effect stems from foreign body reactions around the micro particles	• Effect stems from volume

Differences between bulking agents

• **Chronic foreign body reaction may result in**
  ○ **Encapsulation / hardness**
  ○ **Tissue erosion**
  ○ **Calcification leading to tissue hardness**
	• No adverse tissue changes
	• Hydrogel becomes an integral part of urethra due to vessel bearing connective tissue (hence no necrosis)

• Difficulties in voiding because of fibrosis/cysts	• Any voiding difficulties after injection are transient
• Difficult to inject because of higher viscosity	• Patented injection system • Gel viscosity allows easier injection

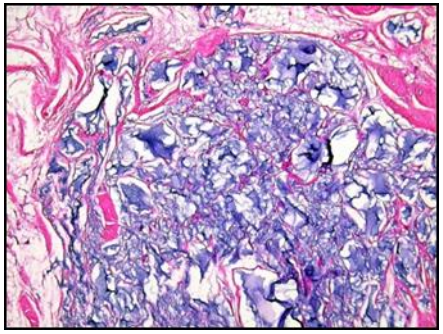
Bulkamid Mode of Action

Lose G

BJU International, 2006

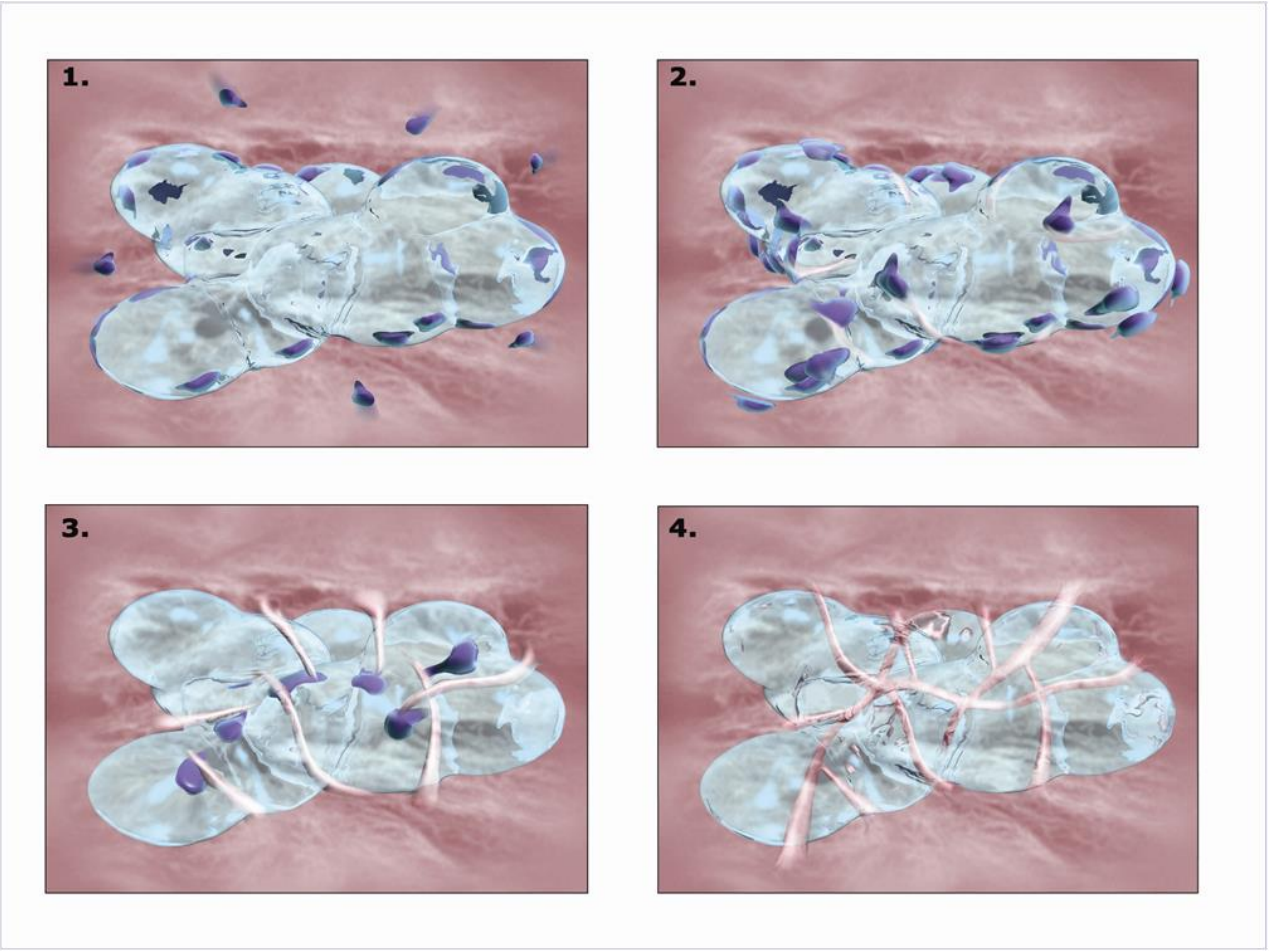
Bulkamid® Hydrogel Features

Bulkamid is a polyacrylamide hydrogel (2.5% cross-linked polyacrylamide and 97.5% water

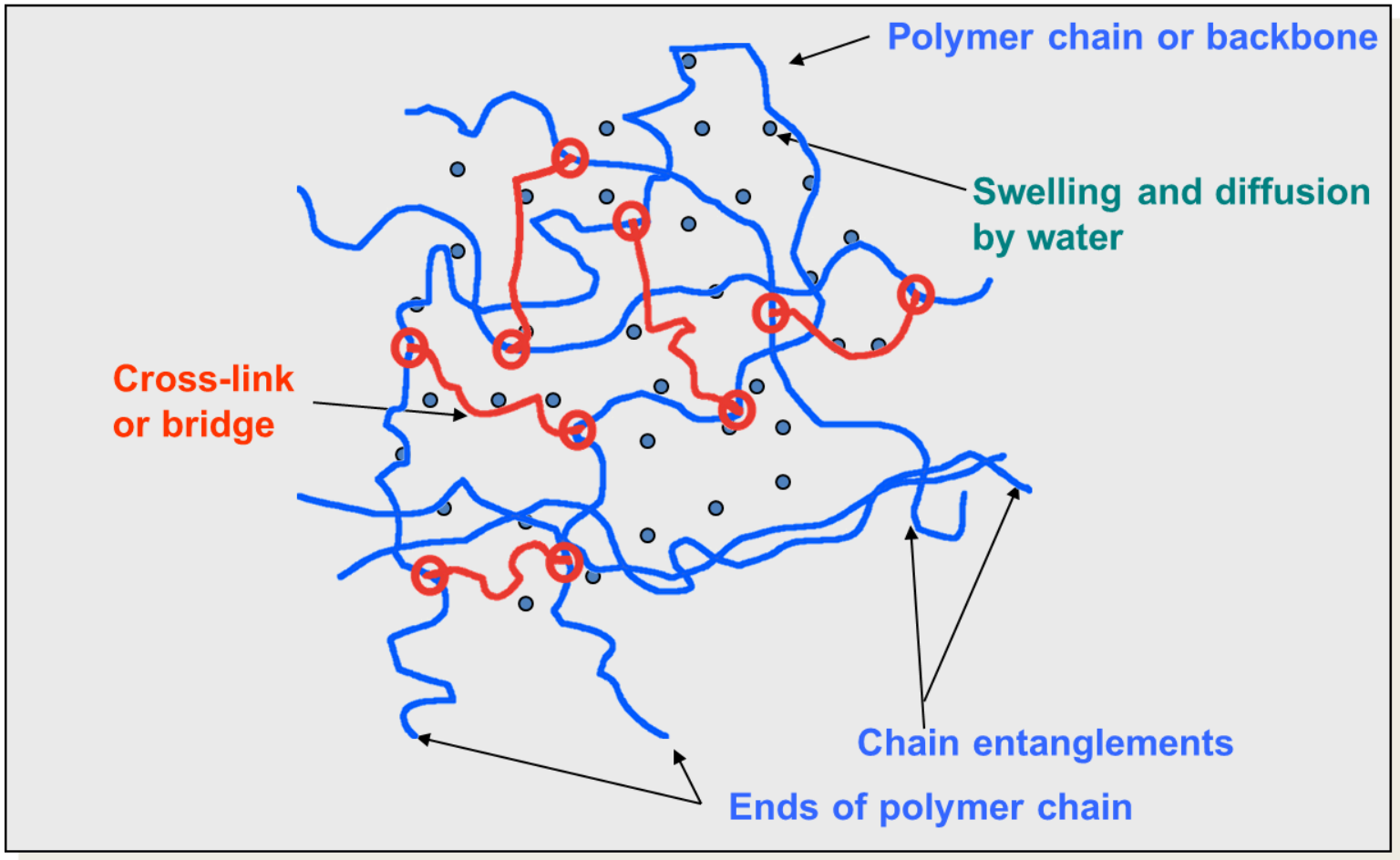


Features	*Advantages*	*Bulkamid*
Biocompatible	Fully accepted by the host tissue	√
Non-Particulate, Homogenous Hydrogel	Does not cause inflammatory reactions avoiding impairment to urethral function	√
No Immunogenicity	No allergic reactions	√
Visco-Elastic Properties	Keeps tissue elastic, maintaining the bulking effect and avoiding tissue hardening	√
Total Tissue Integration	Maintains volume and stays in place over time	√

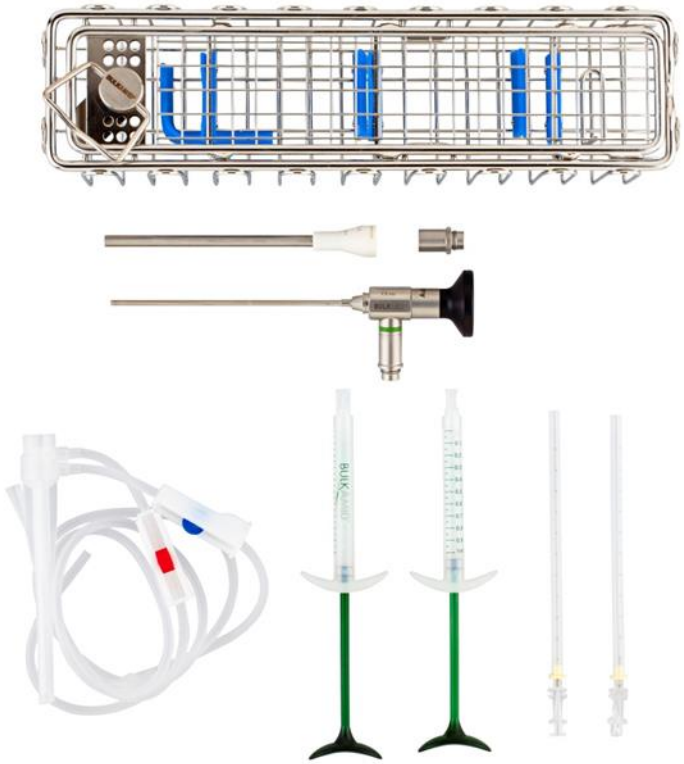
Fine Fibrous Network Formation within the Gel



Bulkamid® Hydrogel Structure



The Bulkamid® products

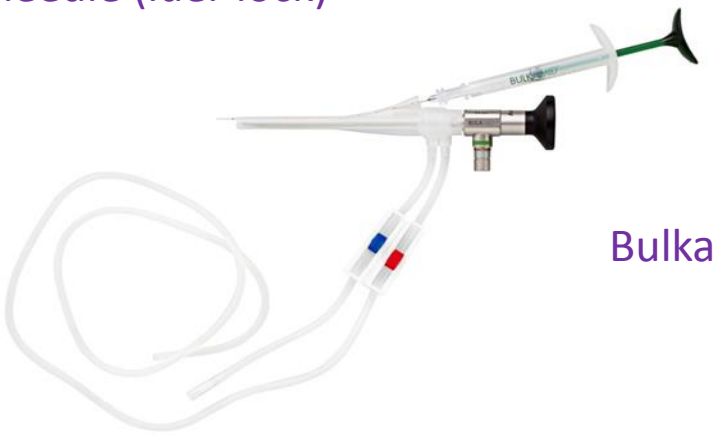


BUOP
Bulkamid 0◦ optic with protection sheeth and light addaptors

Single packed syringes

Assembled Bulkamid® device

Bulkamid® Hydrogel syringe
23 G needle (luer lock)



Bulkamid® Urethroscope

Water connectors
- blue for inlet and red for outlet

Bulkamid® Hydrogel Mode of Action

- Bulkamid's filling effect relies on added volume from the gel itself
- Bulkamid becomes intimately integrated within the tissue via a network of fine fibrous fibers
- The gel stays in place. It does not change in volume or consistency, and it is not disintegrated
- Bulkamid has no micro-particles and is hydrophilic
- It does not elicit an intense foreign body reaction with ensuing scar tissue, erosions and the risk of nodule formation

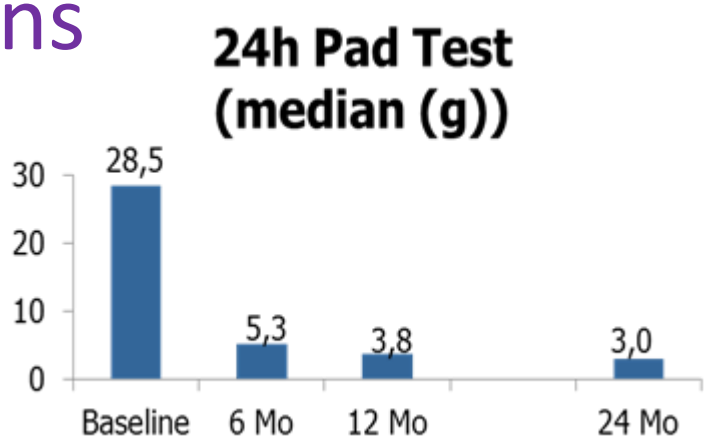
European 2 Year Follow Up of Multi-Centred Trial

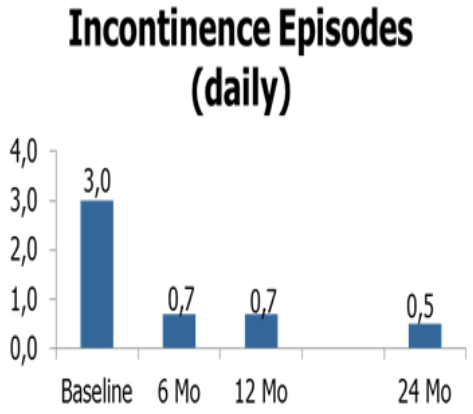
Toozs-Hobson P et al

Int. Urogynecol J, 2012

European 2-year follow up confirms initial effect remains

- Single-arm across 10 sites in Europe
- 135 subjects (67 SUI & 68 MUI patients)
- 24-month follow-up after treatment with Bulkamid®
- Mean total volume injected: 1.5 mL
- 35% received second injection





Results at 24-month follow-up:

- Significant reductions in leakage (89%) and incontinence episodes (83%)
- Subjective responder rate was 64%
- Significant improvement in ICIQ and VAS scores maintained
- No safety issues occurred

Toozs-Hobson P et al Int. Urogynecol J, 2012

North American Bulkamid Study

Sokol et al Int.

Journal of Urology 2014

Sokol E, Karram M, Dmochowski R. Journal of Urology, 2014

North-American Bulkamid Study

Study design

- Adult women with SUI or SUI predominant MUI
- 28 sites in the U.S. and 5 sites in Canada
- 345 women randomized at 2:1 ratio (229 Bulkamid® and 116 Contigen®)
- 87.8% of Bulkamid-treated women and 87.9% of Contigen-treated women completed the study
- Follow up was conducted at 3, 6, 9, and 12 months after the last injection

North-American Bulkamid Study b

Primary endpoint

- At least a 50% reduction from baseline in both:
- Incontinence, as measured by the 24h Pad Test
- Daily number of incontinence episodes

Secondary endpoints

- Responder rate based on the subject perception of effectiveness
- Change from Baseline in IQoL score and ICIQ-UI score

North-American Bulkamid Study

Baseline Characteristic	Bulkamid®		Collagen	
	Median	Min, Max	Median	Min, Max
Age	58.5	23.3, 93.4	56.7	29.5, 85.4
BMI (kg/m^2)	27.6	17.0, 44.5	26.8	18.7, 34.8
Duration of SUI (years)	6.6	0.6, 51.5	5.9	0.7, 39.7
Number of pregnancies	2.0	0.0, 11.0	2.0	0.0, 8.0
Valsalva Leak Point Pressure (cm H_2O)	59.0	8.0, 100.0	54.0	6.0, 102.0
Maximum Cystometric Capacity (ml)	398.0	244.0, 868.0	375.0	150.0, 838.0
Maximum detrusor pressure (cm H_2O)	5.0	0.0, 23.0	5.0	0.0, 22.0
Post-void Residual urine (ml)	10.0	0.0, 200.0	10.0	0.0, 100.0
Leakage (ml)	44.2	0.0, 908.0	40.8	0.2, 2211.4
Incontinence episodes for 3 consecutive days	3.3	0.0, 17.3	3.0	0.7, 13.7

Sokol E, Karram M, Dmochowski R. Journal of Urology, 2014

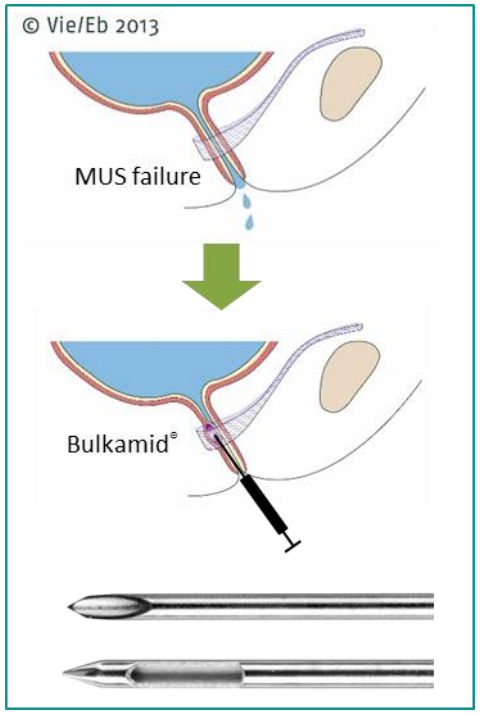
North-American Bulkamid Study

- At 12 months a 50% or greater decrease in leakage and incontinence episodes was seen in 53.2% and 55.4% of patients who received hydrogel and collagen gel, respectively.
- At 12 months 47.2% of patients with hydrogel and 50% with collagen gel reported zero stress incontinence episodes, and 77.1% and 70%, respectively, considered themselves cured or improved.
- Major adverse events were rare in each group.

Urethral Bulking for Recurrent Stress Urinary Incontinence after Midurethral Sling Failure

Zivanovic I,1 Rautenberg O,1 Lobodasch K,2 Crosby DA,3 Von Bünau G,3 Walser C,1 Viereck V1

- Bulkamid®: non-degradable, non-particulate, cross-linked polyacrylamide hydrogel (2.5% dry matter, 97.5% water)
- Used as a bulking agent to treat SUI
- Few retrospective studies on the use of urethral bulking agents for recurrent SUI after midurethral sling (MUS) failure
- Prospective study conducted to assess the efficacy and safety of Bulkamid® in treating recurrent SUI after MUS failure
- Injected at midurethra determined by measured the urethral length
- Modified needle with a blunt tip (12cm, 22G, FemoBulk®)
- Postoperative ultrasound to verify position



Efficacy Results

- 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 (range 1–3 ml)
- Cure rates were assessed objectively and subjectively
- Complications assessed

Post-operative complications:

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

Efficacy Results

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%)

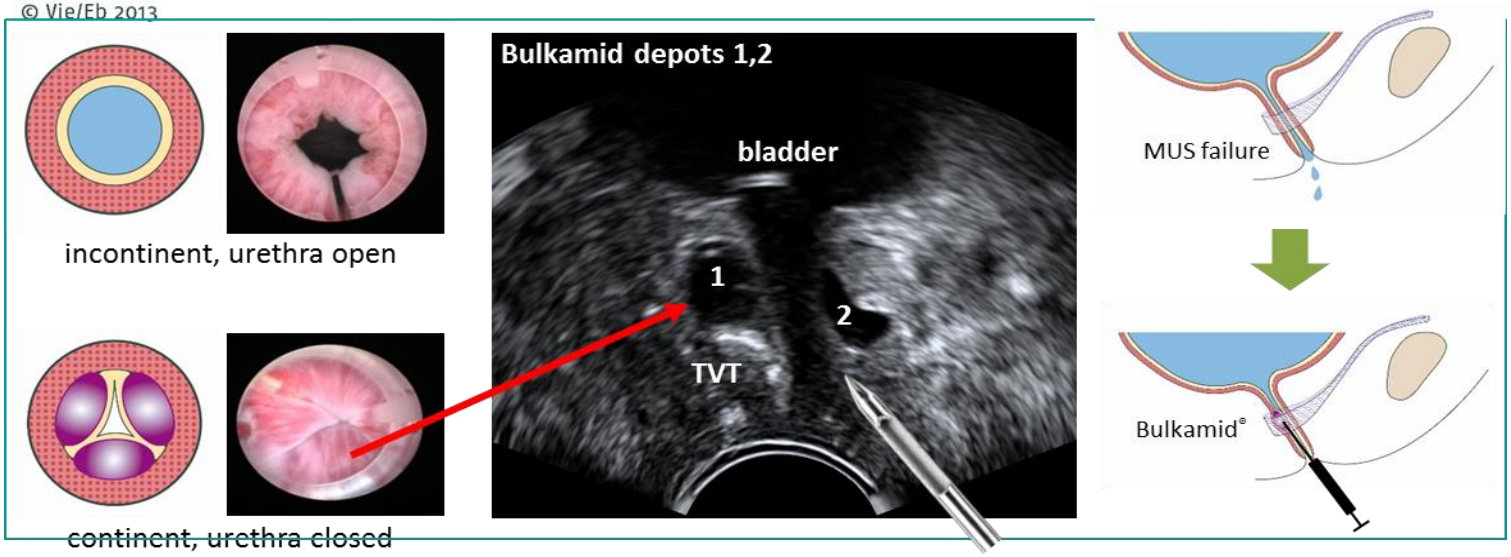
Complications	≤1 month (n=60)	6 months (n=60)	12 months (n=55)
persistent urgency	12 (20%)	10 (17%)	11 (20%)
voiding dysfunction, RU≥100ml	8 (13%)	5 (8.3%)	1 (1.8%)
UTI postop	3 (5.0%)	7 (12%)	2 (3.6%)
de novo urgency	1 (1.7%)	2 (3.3%)	2 (3.6%)

Conclusions

Bulkamid® can be used to treat recurrent SUI after MUS failure with good outcome and low complication rates.

Success rates lower than those reported with salvage MUS treatment, but fewer complications

12 month cured and improved rates of 83.7% are comparable to first-line bulking therapy



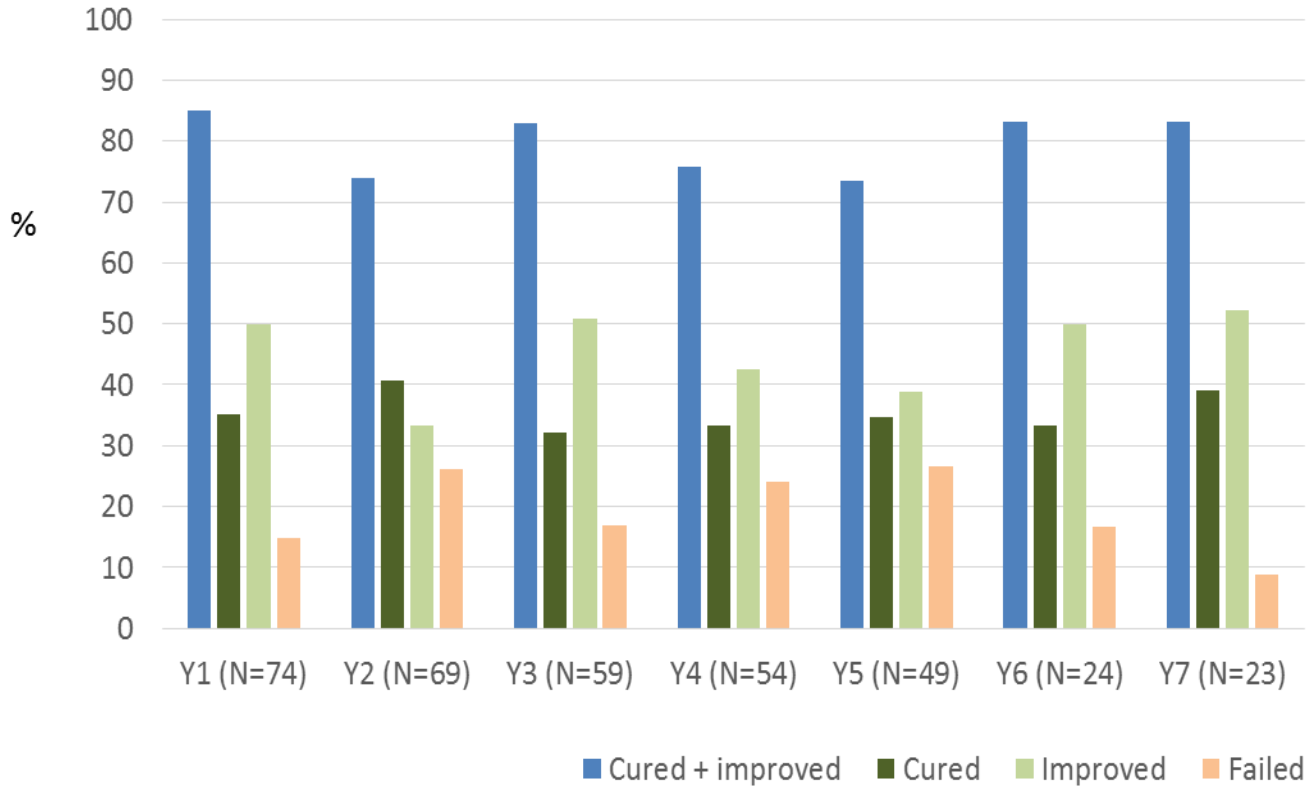
Bulkamid® as 1st line therapy
7 year study at DRK Clinic (Germany)

- 687 patients injected with Bulkamid since October 2005
- Longitudinal study on 352 women (255 SUI and 97 MUI):
- Average age 67 (29-95)
- BMI 30 (17-64)
- Parity 1.9 (0-8)
- Bulkamid procedures represented about 1/3 of all incontinence operationsCured: negative stress test and at least a 90% VAS improvement
- Improved: losing only a few drops during stress test and improvement in VAS of at least 60%
- Failed: urine loss during stress test and a VAS of 50% or less

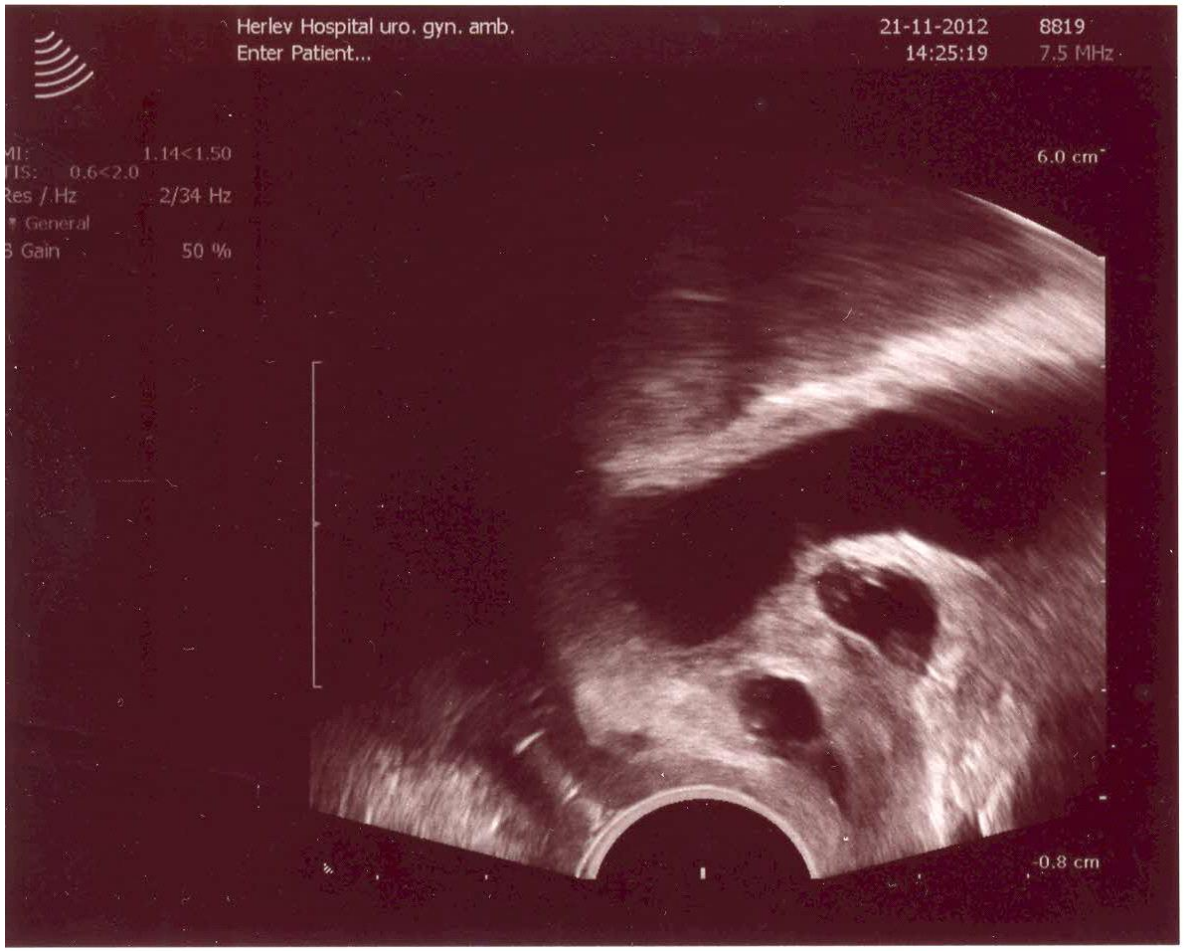
Lobodasch K. Geburtsh Frauenheilk 201; 70; 47-51
Lobodash K. ICS 2012 & ICS 2015 abstracts
Data on file

7 Year Durability of Bulkamid

- Mean use of pads reduced from 4.1 to 1.76 postoperatively
- At the most recent follow up visit 76% of patients described themselves as improved



After 8 years Bulkamid stays where it was injected



Learning Curve and Patient Outcome with Bulkamid

Results

- The learning curve is such that with experience patient outcomes are improved
- Experienced user achieved “cure rate” of 82%
- New User “cure rate” 50%
- With sub-optimal outcome, majority of women opted for top up Bulkamid treatment as opposed to TVT when symptoms of stress incontinence recur

Bulkamid® for mixed UI: a prospective analysis of 122 women

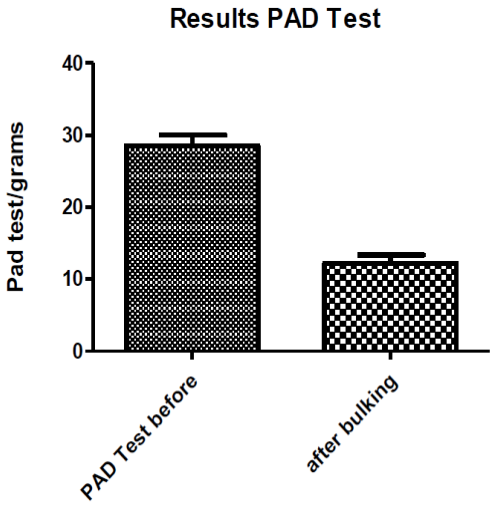
Marthaler C, Mohr S, Imboden S, Monga A, Mueller MD, Kuhn APresented at Swiss Gynaecology Annual Meeting, June 2015

- Methods
- Components of stress urinary incontinence and OAB had to be within the limits of 60%-40% either way to avoid predominance of one aspect.
- Primary outcome: “incontinence impact” of the King’s Health Questionnaire (KHQ)
- Secondary outcomes: other domains of the KHQ, visual analogue scale (VAS), ICS standardized PAD test as objective measurement of incontinence and maximum urethral closure pressure as determined by multichannel urodynamics.
- Subjective and objective outcomes were measured before and three months after intervention.

Bulkamid® for mixed UI: a prospective analysis of 122 women

Results

- Statistically significant improvements were found for the domains: incontinence Impact, general health, role limitations, pad weight test and VAS before and after bulking
- Subjective assessment showed improvements in
- physical and personal limitations as well
- emotions and sleep
- Overall complication rate was less than 3
- UTI: n=2; temporary retention, n=1



Thank You

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