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de Vries A[1], Wadhwa H[2], Huang J[2], Islam M[3], Farag F[4], Heesakkers J[1], Kocjancic E[2]
1. *Radboud University Nijmegen,* ***2.*** *University of Illinois, Chicago, USA,* ***3.*** *University of Missouri School of Medicine, Columbia, USA,* ***4.*** *Department of Urology, Sohag University Hospital, Sohag, Egypt*

COMPLICATIONS ASSOCIATED WITH URETHRAL BULKING AGENTS IN THE TREATMENT OF FEMALE STRESS URINARY INCONTINENCE: AN EXTENSIVE REVIEW INCLUDING CASE REPORTS

Hypothesis / aims of study

Urethral bulking agents have been used for many years in the treatment of female stress urinary incontinence. Searching for an effective and safe product, many products were and are developed. Though there is enough literature describing the clinical results of these -often new- products, there is a lack of high-quality comparative articles. It is these articles however that are necessary for conventional systematic reviews.
When performing a systematic review and/or meta-analysis after the complications of urethral bulking agents, the majority of literature is discarded because it does not meet the inclusion criteria. In our opinion a systematic review is not the optimal way to describe the complications of urethral bulking agents.
The aim of this study was therefore to perform an extensive review of all available literature, including case reports, to get a broader view of the complications encountered with the recently available bulking agents.

Study design, materials and methods

On March 7, 2016, we performed an extensive search in the PubMed, Embase and Cochrane databases. The search was limited to the synonyms or equivalents of “urethra,” “urinary incontinence,” and the different bulking agents. All original articles and case reports describing the complications of urethral bulking agents were included.
We deliberately chose not to perform a systematic review and to also include case reports and small case series. A critical appraisal of the selected articles might be possible and is in agreement with the current scientific standards, but it would also mean excluding a significant part of the available literature. Furthermore, even after critical appraisal the heterogeneity in reported outcomes is so large, that comparison of the different bulking agents, let alone a meta-analysis, would be very difficult to perform. We therefore chose to aspire completeness rather than high validity of included articles.

We included all original Dutch, French, German or English articles describing complications of the treatment of adult females (>18 years) with SUI by means of UBA’s. Case reports and small case series were also included. Exclusion criteria were: 1) treatment of male incontinence, 2) no predominant stress urinary incontinence, 3) stem cell injection, 4) children, animal, and cadaver-studies, and 5) meta-analyses, reviews, or conference papers.

From all articles complications, their treatment and follow-up times were extracted per product. Complications were categorized into retention, pain, hematuria, infection, urinary complaints, periurethral abscess, pseudocyst, pseudoabscess, granuloma or foreign body reaction or unspecified mass, migration, abscess or mass with severe complication (i.e. prolapse, fistula), and erosion of urethra or vaginal wall. Due to difference in semantics throughout the studies, complication treatments were divided into three categories: expectant management, incision and drainage, or invasive treatment.
Subsequently, the complications were classified according to the Clavien-Dindo classification. Complication rates for each of the 8 analyzed urethral bulking agents were calculated. This was done by comparing the reported complications with the number of patients treated in the studies.

Results

We found a cohort of 4,978 unique articles, from which 79 original articles and 38 eligible case reports were retrieved.

Table 2: numbers of articles and patients published per product

Product	Original articles*			Case reports		
	Published articles (N)	Patients treated (N)	Mean follow-up (months)**	Published articles (N)	Patients treated (N)	Mean follow-up (months)**
Bulkamid	14	1052	21 (9-96)	1	1	3 (3-3)
Coaptite	2	141	12 (12-12)	4	5	4 (1-7)
Contigen	37	3173	13 (2-50)	16	23	8 (0-36)
Durasphere	3	326	7 (10-12)	5	5	27 (8-60)
Macroplastique	14	654	29 (3-60)	3	4	14 (14-14)
Tegress	3	156	21 (5-51)	1	2	4 (4-4)
Urolastic	3	127	18 (12-24)	0	0	-
Zuidex	11	833	12 (6-80)	8	10	15 (0-60)
Total	79	6462	19 (2-96)	38	50	11 (0-60)

* in some articles multiple products were investigated; **mean follow-up in articles (range);

Original articles (excluding case reports)

In 6462 treated patient a total of 2095 complications (32%) were reported in the 79 analyzed studies. Of the reported complications, 67 (3%) were considered major (Clavien Grade III - requiring an additional procedure). The remaining 2028 complications were treated with conservative therapy.

Table 4: treatment of complications per product in original articles

	No of treated patients	Total no of complications	Non-invasive Management	Incision & drainage	Invasive surgery	No of Clavien III complications
Bulkamid	1052	189(18%)	188	0	1	1(0.00%)
Coaptite	141	64(45%)	63	0	1	1(0.01%)
Contigen	3173	690(22%)	688	0	2	2(0.00%)
Durasphere	326	80(25%)	76	3	1	4(0.01%)
Macroplastique	654	620(95%)	620	0	0	0(0.00%)
Tegress	156	21(13%)	20	0	1	1(0.01%)
Urolastic	127	31(24%)	17	2	12	14(11.02%)
Zuidex	833	400(48%)	356	41	3	44(5.28%)
Total	6462	2095(32%)	2028	46	21	67(1.04%)

Noninvasive management: includes watchful waiting/antibiotics/CIC/suprapubic tube
invasive surgery: includes excision/reconstruction

Case reports

In 38 case reports and small case series, 50 patients were treated for 50 complications. The complications tend to be more severe, as minor complications are less interesting to report in case reports. Reported treatments are also more invasive than in the original studies. Out of 50 complications, 30 (60.0%) were classified as Clavien Grade III.

Interpretation of results

The advantage of our method is that many articles can be included that would be excluded from other reviews that performed meta-analysis. After our full text assessment, there were only 7 RCT's describing complications and 4 other comparative studies. The remaining 68 articles, comprising of 49 prospective single-arm studies would have been deleted. This shows that an important part of literature would be neglected by the strict rules applying for systematic reviews. By furthermore adding the case-reports another 38 articles were added to the scope of our review. Case reports are an important way to display specific concerns about products in medical literature.

Concluding message

In our review, Bulkamid, Contigen, Durasphere, Tegress and Urolastic have the lowest overall complication rates in original articles. Complications requiring surgical removal were mostly seen with Urolastic and Zuidex, with the other injectables rarely requiring this.

Despite the limitations of our study, we can conclude that most bulking agents currently available seem to have a good safety profile, with low complication rates. Comparison based on efficacy should point out which has the best ratio between efficacy and risk on complications.

Disclosures

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