Maturitas 163 (2022) 28–37

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Urethral bulking agents for the treatment of recurrent stress urinary incontinence: A systematic review and meta-analysis

Andrea Braga [a,b,*], Giorgio Caccia [a], Andrea Papadia [b,c], Giorgio Treglia [b,d,e], Fabiana Castronovo [a], Stefano Salvatore [f], Marco Torella [g], Fabio Ghezzi [h], Maurizio Serati [h,i]

[a] Department of Obstetrics and Gynaecology, EOC - Beata Vergine Hospital, Mendrisio, Switzerland
[b] Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland
[c] Department of Obstetrics and Gynaecology, EOC – Civico Hospital, Lugano, Switzerland
[d] Academic Education, Research and Innovation Area, General Directorate, Ente Ospedaliero Cantonale, Bellinzona, Switzerland
[e] Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland
[f] Department of Obstetrics and Gynaecology, IRCSS San Raffaele Scientific Institute, Milan, Italy
[g] Department of Gynaecology, Obstetric and Reproductive Science, Second University of Naples, Naples, Italy
[h] Department of Obstetrics and Gynaecology, Del Ponte Hospital, University of Insubria, Varese, Italy
[i] President of European Urogynaecological Association (EUGA), Italy

ARTICLE INFO

Keywords:
Urethral bulking agent
Recurrent stress urinary incontinence
Persistent stress urinary incontinence
Mid-urethral sling failure
Female urinary incontinence

ABSTRACT

Recurrent stress urinary incontinence (rSUI) represents a major challenge for most clinicians as there is little evidence in the literature on the best option after sling failure. The objective of this study is to summarise the findings on the use of urethral bulking agents (UBAs) in the management of rSUI after the failure of a mid-urethral sling (MUSs). We performed a systematic review and meta-analysis, according to PRISMA 2020 guidelines, and selected eleven publications for inclusion in the analysis. We found that the overall cure and improvement rate ranged from 64% to 85% in the included studies, with a pooled value of 75%, compared with pooled failure and re-operation rates of 32% (95% CI: 22%–43%) and 25% (95% CI: 17%–34%), respectively. The I^2 test indicated significant statistical heterogeneity among the studies in relation to all the outcome measures; however, no risk of publication bias was found. To explore this heterogeneity in more depth, we performed a sub-group analysis of the two most commonly used bulking agents (Bulkamid and Macroplastique). The pooled values of the cure and improvement rate were 84% (95% CI: 77.0%–90.0%) and 80% (95% CI: 74.0%–85.0%) for Macroplastique and Bulkamid, respectively. We did not find significant heterogeneity or significant differences in the outcome measures in either group.

For the first time in literature, our study provides an insight into the use of UBAs after failed MUSs. Although the results seem very promising, future studies with shared protocols are needed in order to recommend the use of UBAs in the treatment of recurrent cases.

1. Introduction

Over the past twenty years, Mid-Urethral Slings (MUSs) have become the most popular surgical procedure for female Stress Urinary Incontinence (SUI), with excellent subjective and objective cure rates in the medium to long term [1,2]. However, the failure rate after MUS, has been reported to be 5% - 20% of previously treated patients [3,4].

Recurrent Stress Urinary Incontinence (rSUI) represents a major challenge for most clinicians. Unfortunately, there is a lack of robust evidence in literature regarding the best option available after sling failure. In 2017, a Cochrane Collaboration Review was unable to find enough high-quality data to assess the effects of any of the management strategies for rSUI after failed MUS [5]. A global survey of experienced urogynaecological clinicians and members of the International Urogynaecological Association (IUGA) could not even fill this knowledge gap [6]. Consequently, to date, there is a significant variation in the use of second-line surgical treatments depending on the surgeon's experience.

Repeat MUS is still the most common option used in these

* Corresponding author at: Dept. Obstetrics and Gynaecology, EOC - Beata Vergine Hospital, Via Alfonso Turconi 23, 6850 Mendrisio, Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland.
E-mail address: andrea.braga@eoc.ch (A. Braga).

https://doi.org/10.1016/j.maturitas.2022.05.007
Received 10 March 2022; Received in revised form 30 April 2022; Accepted 16 May 2022
Available online 26 May 2022

circumstances. Data from non-randomised control trials (RCT) report cure rates of 73–79% for repeat MUS, with the retropubic route possibly being more effective than the transobturator route [7]. Recently, Urethral Bulking Agents (UBA), colposuspension and autologous fascial slings are being considered again, due to the complications arising from the use of mesh [3,6,8]. In fact, in light of the recent announcement of the British government, the use of MUSs for female SUI has come under scrutiny, also in primary surgery.

In this scenario, the patients' perspective is to avoid repeating a previously unsuccessful surgery, and UBA, due to its minimal invasiveness, is often favoured by patients as the next step to improve SUI [7,9]. Data from several case series on the use of UBA after MUS failure appears to be encouraging. These studies have reported that subjective cure and improvement rates are relatively high in the short-term follow-up.

The aim of this systematic review and meta-analysis is to summarise the main findings of the use of UBAs in the management of rSUI after failed minimally-invasive synthetic mid-urethral tape surgery in women.

2. Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [10]. The protocol was not registered in PROSPERO, but an internal protocol was created before performing the meta-analysis according to PRISMA guidelines.

2.1. Eligibility criteria

In our analysis we included the available studies that evaluated the (subjective and objective) efficacy of (all types of) urethral bulking agents for the treatment of female recurrent and/or persistent SUI after previous MUS failure.

The following epidemiological designs were considered suitable: RCTs and observational prospective or retrospective cohort studies. We excluded: review articles, case reports, commentaries, editorials, meeting abstracts and studies with $\leq$10 patients. The search was conducted without any restrictions regarding the year of publication or language.

2.2. Information source

A systematic literature search was performed using the PubMed/MEDLINE (Medical Literature Analysis and Retrieval System Online) and CENTRAL (Cochrane Central Register of Controlled Trials) databases (last search date: 31 December 2021).

2.3. Search strategy

The terms used alone or in combination for the literature search were:

a) “Bulking agent”; AND
b) “recurrent stress urinary incontinence” OR “persistent stress urinary incontinence”; AND
c) “female” OR “women”; AND
d) “failed mid-urethral sling” OR “mid-urethral sling failure” OR “tension-free vaginal tape failure” OR “failed tension-free vaginal tape”.

All pertinent articles were carefully evaluated and their reference lists were examined in order to identify other manuscripts that could be retrieved in this review.

2.4. Selection process

A narrative synthesis and a quantitative analysis (meta-analysis) were performed. Two independent reviewers (A.B. and F.C.) selected each article being considered, through titles and abstracts, and excluded unrelated studies. Discrepancies were resolved by consensus, including a third author (M.S.), who checked the eligible studies. If multiple publications for the same research group were found, data from the largest sample was used. Afterwards, potential eligible studies were assessed in full-text to decide whether to include them in the qualitative and quantitative analysis.

2.5. Data collection

Structured tables were used to extract necessary data from each eligible study. The data extracted included: authors' names, year of publication, study design, country, type of bulking agent, type of mid-urethral sling, age of patients, Body Mass Index (BMI), menopausal status, parity, type of incontinence, type of subjective and objective assessment, subjective and objective cure rate, cure and improvement rate, failure rate, re-operation rate and months of follow-up.

2.6. Data items

- Subjective outcomes were evaluated through self-reported symptoms and validated questionnaires.
- Objective outcomes were evaluated through cough and Valsalva stress tests, pad tests and voiding diaries.
- Improvement rates were evaluated through self-reported symptoms and the need for further interventions due to incontinence.

2.7. Study risk of bias assessment

The assessment of the methodological quality of the cohort studies included in this review was performed independently by two authors (A. B. and M.S) using the Newcastle-Ottawa Scale (NOS), scoring across three categories: studies with 7–9 stars were considered of low Risk of Bias (RoB), studies with 5–6 stars of moderate RoB, while studies with less than 5 stars were considered of high RoB. Any doubts were resolved by discussion with a third author (F.C.).

2.8. Statistical analysis

Continuous variables were expressed as absolute and relative (percentage) values. A proportional meta-analysis was performed for several outcome measures (cure and improvement rate, failure rate and re-operation rate) and Forest plots were used to graphically display the estimated results. A random-effects model [11] was used for the statistical pooling of data. Results were reported as a pooled percentage with related 95% confidence intervals (95%-CI). Heterogeneity between studies was based on the Higgins I^2 index [12], with I^2 values of >50% being considered to indicate the presence of heterogeneity [12,13]. Egger's test and funnel plots were used for an evaluation of publication bias [14], with a *p*-value of less than 0.05 being considered statistically significant. Sub-group analyses were performed when significant heterogeneity among the included studies was detected and statistical analysis was performed using StatsDirect version 3 software (StatsDirect Ltd., Birkenhead, UK).

3. Results

3.1. Study selection

We identified 1187 records up to 31 December 2021. After the exclusion of 494 publications (295 removed for duplication, 178 marked as ineligible and 21 excluded for other reasons), 693 original articles

were selected for screening. Among these, only 12 met the inclusion criteria. One study was excluded because it was a conference paper. At the end of the selection process, 11 studies were selected for qualitative and quantitative analysis. The detailed process is reported in Fig. 1.

3.2. Study characteristics

Eleven published studies including 542 patients undergoing UBA procedure after MUS failure were included in this systematic review and meta-analysis [15–25]. The study design and basic characteristics of the patients are reported in Table 1.

Seven out of 11 studies were retrospective observational studies [15-17, 120, 21, 23, 25], whereas four had a prospective design [18,19,22,24]. All but one [24] were monocentric studies, from nine different countries, across North America, Europe and South Korea. Bulkamid was the most commonly-used bulking agent [211 patients (38.9%)], followed by Macroplastique [168 patients (30.9%)] and Urolastic [66 patients (12.2%)]. The remaining 18% (97 pts) included Collagen [35 patients (6.5)], Contigen [33 patients (6.2)], Coaptite [27 patients (4.9)] and Durasphere [2 patients (0.5)]. In the majority of cases [451 patients (83.2%)] UBA was performed after failure of Retropubic Tension-free Vaginal Tape (TVT) and/or Tension-free Vaginal Transobturator Tape (TVT-O). Several procedures [91 patients (16.8%)] were followed after other types of MUSs, such as Innovative Replacement of Incontinence Surgery (IRIS), Single Incision Sling (SIS), anterior Intravaginal Slingplasty (IVS) and Autologous Fascial Sling (AFS).

Seven studies considered women with pure SUI [15,16,18,21–24], while four studies included also women with Mixed Urinary Incontinence (MUI) and predominant SUI [17,19,21,25]. The sample size was variable, ranging from 17 [20] to 73 [21] patients. The mean age of the overall sample size was 64 years, ranging from 52 [15] to 71.7 [19] years, while mean BMI was 27.9 kg/m2 ranging from 24.5 [15] to 30.1 [21] kg/m2. Only four studies reported data on menopausal status [15,16,22,24], which on average occurred in 62.8% of patients (23.9–92.8), and parity [17,18,22,24], which ranged from 1.91 to 2.4. The mean follow-up was 20.9 months with a range from 4 [21] to 56 [23] months.

Outcome measures of the studies included in the systematic review

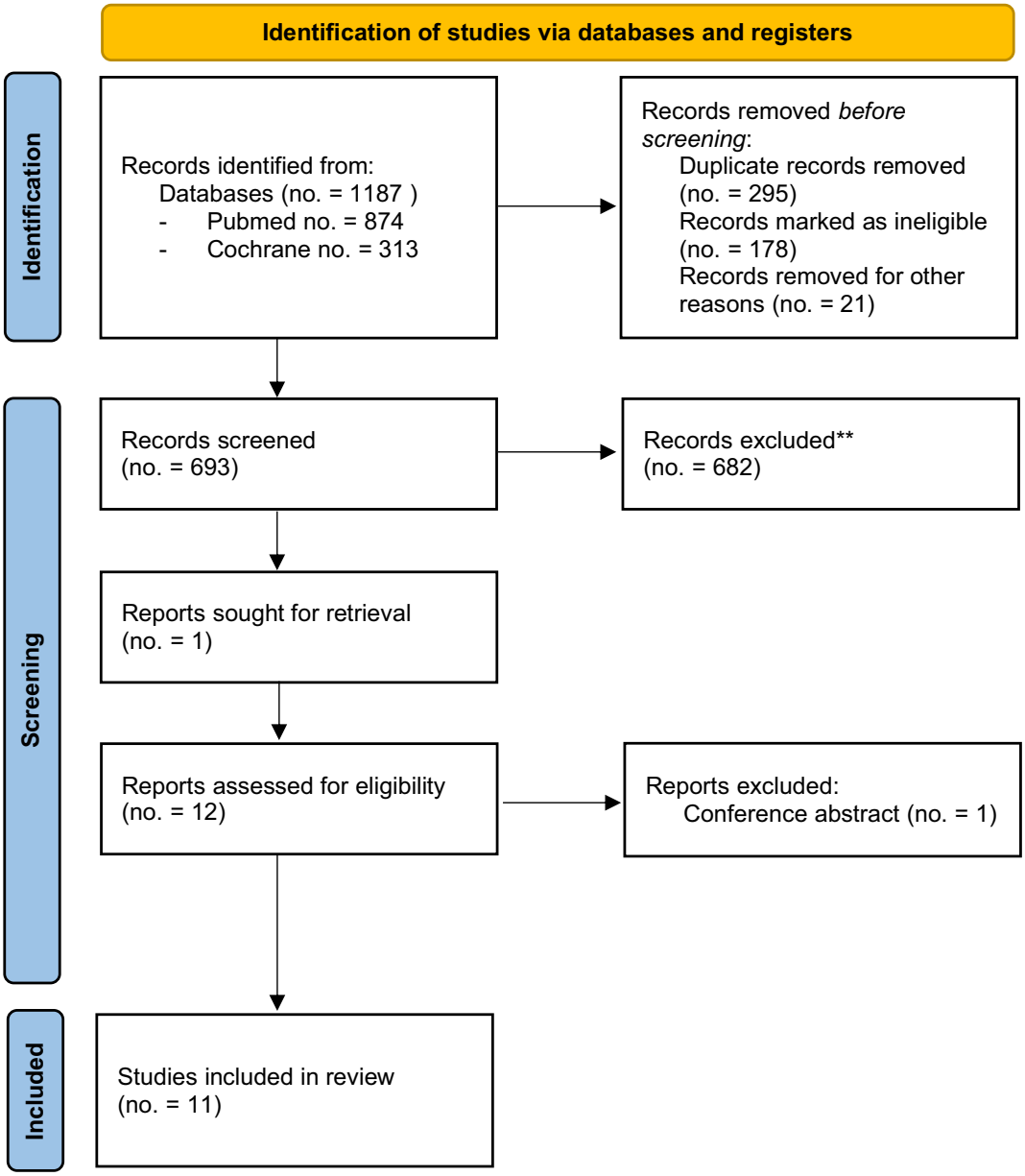


Fig. 1. Flow diagram of evidence acquisition in a systematic review on urethral bulking agents for the treatment of recurrent stress urinary incontinence.

Table 1
Characteristics of the studies and basic characteristics of the patients included in the systematic review and meta-analysis.

Authors	Year	Sample size (N)	Study design	Mono/ Multi -center	Country	Bulking agent	Previous MUS	Type of UI	Mean age (range) ± SD	Menopause (%)	Parity (range) ± SD	Mean BMI (range) ± SD
Lee et al.	2010	23	Retrospective	Monocenter	South Korea	Macroplastique Durasphere	TVT TVT-O IRIS IVS	SUI	52 (44–77)	10 (43.5)	–	24.5
Gaddi et al.	2014	67	Retrospective	Monocenter	USA	Macroplastique Contigen Coaptite	TVT TVT-O SIS	SUI	62.3 ± 13.85	16 (23.9)	–	28.1. ± 5.73
Martan et al.	2015	34	Retrospective	Monocenter	Cechia	Bulkamid	TVT TVT-O TVT-S	SUI/ MUI	71.03 (23–92) ± 13.88	–	1.91 ± 0.87	29.12 ± 4.06
Futyma et al.	2016	66	Prospective	Monocenter	Poland	Urolastic	TVT TVT-O	SUI	65.5 ± 9.2	–	2.8 (0–6)	28. 8 ± 5.7
Zivanovic et al.	2017	60	Prospective	Monocenter	Switzerland	Bulkamid	TVT TVT-O TVT-S SIS	SUI/ MUI	71.7 ± 10.7	–	–	28.8 (±3.9)
Clark et al.	2017	17	Retrospective	Monocenter	Canada	Bulkamid	-TVT -TVT-O -AFS	SUI/ MUI	70 (59–78)	–	–	–
Dray et al.	2018	73	Retrospective	Monocenter	USA	Macroplastique Collagen	MUS AFS	SUI	65.1 (37–91) ±12.6	–	–	30.1 (±7.1)
Rodríguez et al.	2019	70	Prospective	Monocenter	USA	Macroplastique	TVT TOT Miniarc	SUI	62.7 ± 10.7	65 (92.8)	2.4 ± 1.2	27.2 ± 5.9
Daly et al.	2020	28	Retrospective	Monocenter	Scotland	Macroplastique Bulkamid	MUS Fascial sling	SUI	60	–	–	30
Serati et al.	2021	47	Prospective	Multicenter	Italy Switzerland	Macroplastique Bulkamid	TVT TVT-O SIS	SUI	64 (50–69)	43 (91)	2 (1–2)	24.8 (23–28)
Myhr et al.	2021	57	Retrospective	Monocenter	Norway	Bulkamid	TVT	SUI/ MUI	59.7 (36–88) ±13.47	–	–	27.5 (19.5–42) ±5.07

AFS: Autologous Fascia Sling; IRIS: Innovative Replacement of Incontinence Surgery; SIS: Single Incision sling; TVT: Tension-free Vaginal Tape; TVT-O: Tension-free Vaginal Obturator Tape; UI: Urinary Incontinence.

and meta-analysis are reported in Table 2.The cure rate after UBA was provided by 9 out of 11 studies (81.8%) [15–19,21,22,24,25], while overall studies reported the cure plus improvement rate and failure rate. The re-operation rate was reported by 9 studies (81.8%) [15,16,18,20–25]. All studies used a subjective evaluation of results, based on: validated urinary incontinence questionnaires [8 out of 11 studies (72.7%)] [15,17,20–25]; validated QoL questionnaires [3/11 (27.3%)] [16,22,23]; and self-reported symptoms [3/11 (27.3%)] [15,22,25]. An objective evaluation was performed in 7 out of 11 studies (63.6%), with a Cough or Valsalva stress test [5/11 (45.4%)], Pad test [5/11 (45.4%)], and micturition diary [2/11 (18.2%)].

3.3. Risk of bias in studies

Five studies [16,17,20,22,24] presented a low Risk of Bias (RoB) (with 7/9 scores). All the other studies [15,18,19,21,23,25] presented a moderate RoB (three with a score of 6/9, one with 5/9 and two with 4/9) (Fig. 2 and Table 3). The main reason for bias was the representativeness of the cases (two articles with a high RoB and three articles with a moderate RoB). All the studies failed to include the selection of controls. In the ascertainment of exposure, 9 out of 11 (81.8%) studies presented a low RoB. Most of the articles adopted an adequate assessment of outcomes and follow-up evaluations.

3.4. Results of synthesis

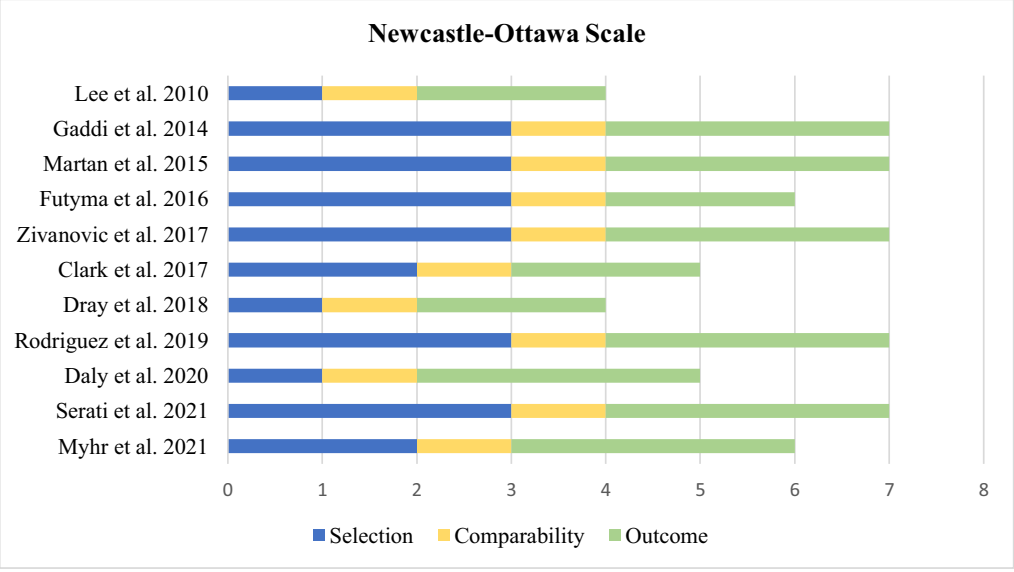
The overall cure and improvement rate ranged from 64% to 85% in the included studies with a pooled value of 75%. The related I^2 – test result was 88.9% (95%CI = 82.5% to 92.3%), demonstrating significant statistical heterogeneity among the studies (Fig. 3a). However, the risk of publication bias was not found through a visual analysis of the funnel plot (Fig. 3b) and the Egger's test, which produced a result of −0.18 (95%CI = −11.2 to 10.8; p = 0.97). The overall failure rate ranged from 22% to 43% with a pooled value of 32%. Here, the I^2 – test result was 85.6% (95%CI = 75.5% to 90.3%), which was representative of significant statistical heterogeneity among the studies (Fig. 4a). A visual analysis of the funnel plot (Fig. 4b) did not show significant asymmetry, and the presence of publication bias is not demonstrated by the Egger's test, which produced a result of 5.74 (95%CI = −1.44 to 12.9; p = 0.10). The overall re-operation rate ranged from 17% to 34% with a pooled value of 25%, which was found in all but two studies [17,19] and, in this case, the I^2 – test result was 76.7% (95%CI = 48.9% to 86.3%), demonstrating significant statistical heterogeneity (Fig. 5a). No significant publication bias was found through a visual analysis of the funnel plot (Fig. 5b) and Egger's test, which produced a result of 3.82 (95%CI = −0.03 to 7.67; p = 0.051).

To explore the aspect of heterogeneity in more depth, we performed a sub-group analysis of the two most commonly-used bulking agents (Bulkamid and Macroplastique). The pooled cure and improvement rate was 84% (95% CI: 77.0% - 90.0%) and 80% (95% CI: 74.0% - 85.0%) for Macroplastique and Bulkamid, respectively. We did not find significant heterogeneity in either of the groups [Macroplastique (I^2 = 0%) and Bulkamid (I^2 = 5%)]. The pooled Macroplastique failure rate was 40% (95% CI: 19% - 63%) with significant statistical heterogeneity (I^2 = 80%), whereas the pooled Bulkamid failure rate was 20% (95% CI: 14% - 26%) without substantial heterogeneity (I^2 = 14%). The pooled re-operation rate was 34% (95% CI: 20.0% - 43.0%) and 24% (95% CI: 13.0% - 37.0%) for Macroplastique and Bulkamid, respectively. No

Table 2
Outcome measures of the studies included in the systematic review and meta-analysis.

Authors	Cure rate %(N)	Cure and Improvement rate %(N)	Failure rate %(N)	*Re*-operation rate %(N)	Follow-up (months)	Subjective assessment	Objective assessment
Lee et al.	34.8 (8/23) (S)	92 (21/23)	65.2 (15/23)	33.3 (5/23)	10	- Sandvik questionnaire - VAS - I-QOL questionnaire - BSWC questionnaire	–
Gaddi et al.	61.2 (41/67) (S + O)	79 (56/67)	38.8 (26/67)	38.8 (26/67)	12	- Self-report symptoms of SUI	- Cough or Valsalva stress test - No retreatment for SUI
Martan et al.	41.2 (14/34) (S) 11.8 (4/34) (O)	88.2 (30/34)	11.8 (4/34)	–	6	- ICIQ-UI SF questionnaire - VAS	–
Futyma et al.	32.7 (16/66) (S + O)	32.7 (16/66)	67.3 (33/49)	10.6 (7/66)	24	- VAS - Stamey Incontinence Scale	- Cough or Valsalva stress test - Pad test.
Zivanovic et al.	25.4 (14/55) (S + O)	83.6 (46/55)	16.4 (9/55)	–	12	- VAS	- Cough or Valsalva stress test - 3-day micturition diary - 1-h pad test.
Clark et al.	–	71 (12/17)	29.4 (5/17)	42 (5/12)	12	- ICIQ-UI questionnaire	–
Dray et al.	24.7 (18/73) (S + O)	71.3 (52/73)	28.8 (21/73)	12.3 (9/73)	4	- AUAS index - M-ISI Index	- Pad test
Rodríguez et al.	46 (32/70) (S + O)	83 (58/70)	54.2 (38/70)	38.5 (27/70)	46	- Self-report of improvement - UDI - Short Form 6 - VAS QoL	- Pad test
Daly et al.	–	75 (21/28) (S)	25 (7/31)	36 (10/28)	56	- Patient reported outcomes scale adapted from the BSUG audit database - ICIQ-UI SF questionnaire	–
Serati et al.	81(38/47) (S) 83(39/47) (O)	83(39/47)	10.6 (5/47)	23.4 (11/47)	36	- ICIQ-UI SF questionnaire - UDI. - PGI-I Scale	- Cough or Valsalva stress test
Myhr et al.	22.8 (13/57) (S) 72.9 (35/48) (O)	73.7 (42/57)	26.3 (15/57)	15.7 (9/57)	12	- SI index score questionnaire - UI index score questionnaire - QoL index score questionnaire	- Cough or Valsalva stress test - Pad test, - 24-h voiding diary

(S): subjective cure rate; (O): objective cure rate; VAS: Visual Analogue Scale; I-QOL: Incontinence Quality of Life; BSWC: Benefit, Satisfaction and Willingness to Continue; ICIQ-UI SF: International Consultation on Incontinence Questionnaire - Urinary Incontinence Short form; AUAS: American Urological Association Symptom; M-ISI: Michigan Incontinence Symptom; UDI: Urogenital Distress Inventory; QoL: Quality of Life; BSUG: British Society of Urogynaecology; PGI—I: Patient Global Impression – Improvement; SI: Stress Incontinence; UI: Urinary Incontinence.



We scored the studies across three categories: studies with 7–9 stars were considered of low Risk of Bias (RoB), studies with 5–6 stars of moderate RoB, whilst studies with less than 5 stars were considered of high RoB.

Fig. 2. Detailed Newcastle-Ottawa Scale of each included cohort study
We scored the studies across three categories: studies with 7–9 stars were considered of low Risk of Bias (RoB), studies with 5–6 stars of moderate RoB, while studies with less than 5 stars were considered of high RoB.

Table 3
Detailed Newcastle-Ottawa Scale of each included cohort study.

Study	Selection				Comparability		Outcome			Total quality score
	Representativeness of the intervention cohort	Selection of the non-intervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of study	Adjustment for the most important risk factors	Adjustment for other risk factors	Assessment of outcome	Follow-up length	Loss to follow-up rate	
Lee et al. 2010	0	0	0	★	★	0	0	★	★	4★
Gaddi et al. 2014	★	0	★	★	★	0	★	★	★	7★
Martan et al. 2015	★	0	★	★	★	0	★	★	★	7★
Futyma et al. 2016	★	0	★	★	★	0	★	★	0	6★
Zivanovic et al. 2017	★	0	★	★	★	0	★	★	★	7★
Clark et al. 2017	0	0	★	★	★	0	★	★	0	5★
Dray et al. 2018	0	0	0	★	★	0	★	0	★	4★
Rodríguez et al. 2019	★	0	★	★	★	0	★	★	★	7★
Daly et al. 2020	0	0	★	★	★	0	★	★	★	6★
Serati et al. 2021	★	0	★	★	★	0	★	★	★	7★
Myhr et al. 2021	0	0	★	★	★	0	★	★	★	6★

significant statistical heterogeneity was found in either of the sub-groups ($I^2 = 33\%$; $I^2 = 46\%$) (Table 4).

The sub-group analyses demonstrated that the heterogeneity among the included studies can be partially explained by the different bulking agents used. Furthermore, there were no statistically-significant differences between Macroplastique and Bulkamid in the outcome measures evaluated.

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis in literature that investigates the efficacy of UBA for the treatment of rSUI. Our study shows that UBAs present a promising cure and improvement rate with acceptable failure and re-operation rates.

To date, as reported by Bakali et al. in a Cochrane Collaboration review [5], there is insufficient data to assess the effects of the different management strategies for recurrent or persistent SUI after failed mid-urethral tape surgery. This lack of evidence is a considerable problem for physicians, who currently have to base their choice of treatment on clinical experience and personal preference. The implantation of a second MUS is the preferred treatment strategy for most clinicians, although success rates are generally considered to be lower than the success rate after a primary sling procedure [26]. In addition, following the warning issued by the United States Food and Drug Administration (FDA) [27] and the recent announcement by the British government, which has paused the use of mesh for pelvic organ prolapse (POP) and SUI, other procedures needed to be considered. As shown by the survey of IUGA members [6], a UBA (with Retropubic sling) is the most common operation offered by the respondents, especially in the absence of urethral hypermobility and in patients with intrinsic sphincter deficiency (ISD). Unfortunately, only a few cohort studies in literature have investigated the efficacy of UBAs as a salvage therapy following a previous MUS. In our systematic review and meta-analysis, we attempted to summarise the efficacy of UBA after failed MUS, which may be useful for surgical decision-making.

The point of strength of this study is the exhaustive analysis of the available literature based on a rigorous methodological process and the specific inclusion of exclusion criteria. In addition, an accurate assessment of the quality of the original studies was carried out using the Newcastle-Ottawa Scale.

Although we found a significant level of heterogeneity among the studies, the overall success rate of UBAs is promising. Seventy-five percent of patients declared themselves cured or improved, whereas only a quarter of these patients with more complicated cases required a subsequent intervention. Furthermore, the complications reported by the different studies are minimal and without long-term effects, such as transitory voiding dysfunction, urinary infection and de novo overactive bladder (OAB) [15–25].

Possible explanations for the heterogeneity of the studies are: 1) the wide variability in the methodological design; 2) the different types of bulking agents; and 3) the several definitions of subjective and objective satisfaction used in the studies. In fact, when we performed a sub-group analysis on the most commonly-used bulking agents [15,17,19,20,22,24,25], the heterogeneity disappeared and the pooled cure and improvement rates were higher than the overall analysis [Bulkamid (80%) and Macroplastique (84%)]. Another considerable strength of the study is that we did not find a significant publication bias in the overall and sub-group meta-analyses.

The limitations of this systematic review and meta-analysis, which reflect the limitations of the available literature on this topic, include: 1) the lack of RCTs and/or case-control group studies; 2) the use of different bulking agents; 3) small and heterogeneous sample sizes; 4) the lack of a clear definition of the subjective and objective cure and improvement rate; and 5) the lack of analysis of how cure rates decrease over time. Unfortunately, with respect to this last point, we do not have sufficient data from the included articles to calculate these rates.

Our suggestions for future research are: 1) RCTs that compare UBAs to other surgical procedures for the treatment of rSUI; and 2) RCTs that

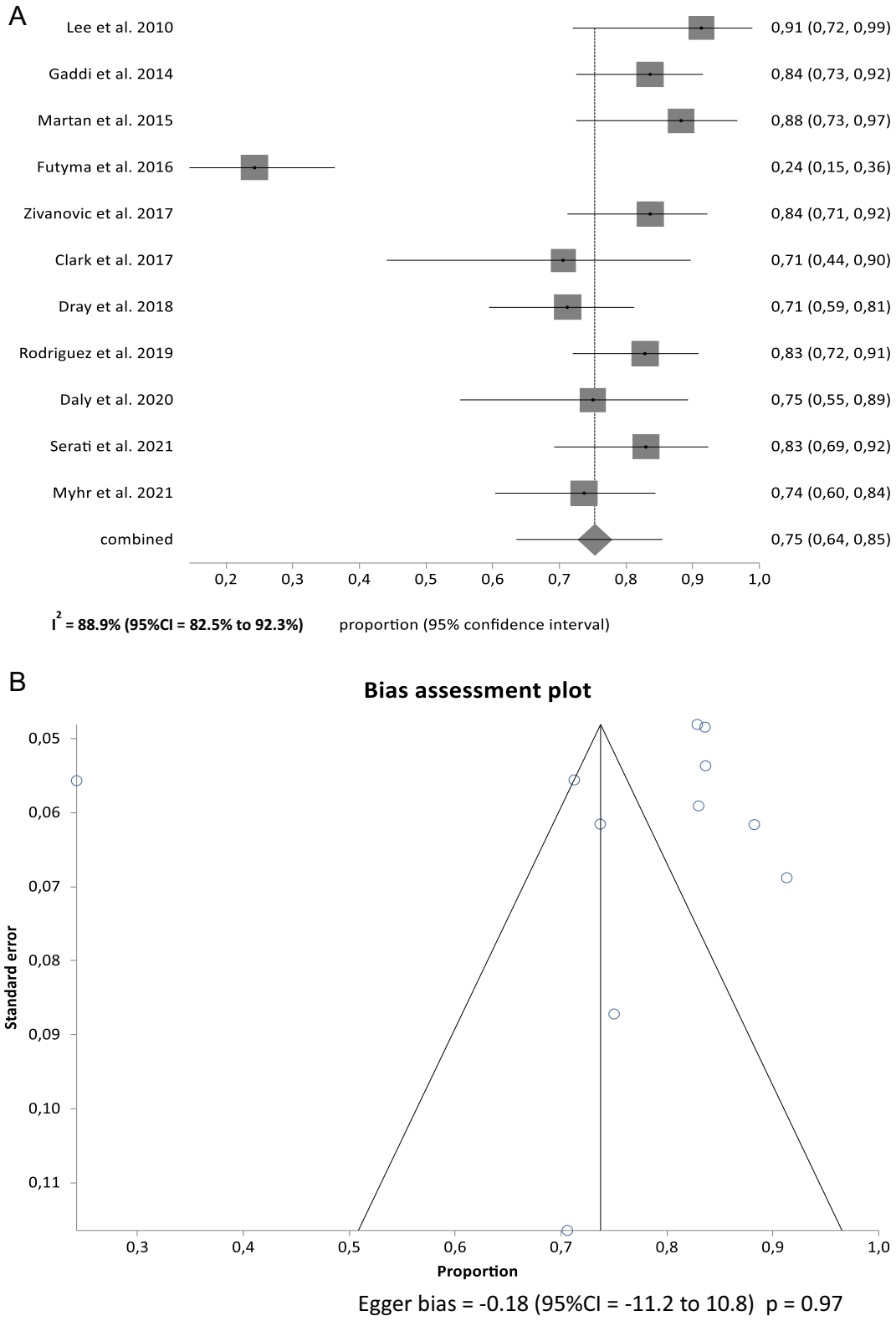


Fig. 3. a. Cure and improvement rate (proportion meta-analysis plot - random effect)
b. Cure and improvement rate (Bias assessment plot).

compare different UBAs for the treatment of rSUI.

5. Conclusions

There is a wide spectrum of surgical interventions available after MUS failure, but there is still no consensus on which salvage procedure should be selected. Despite limitations due to the combination of results from heterogeneous study designs, for the first time in literature, our study provides an insight into the use of UBAs after failed MUS. Although the results seem very promising, future studies with shared

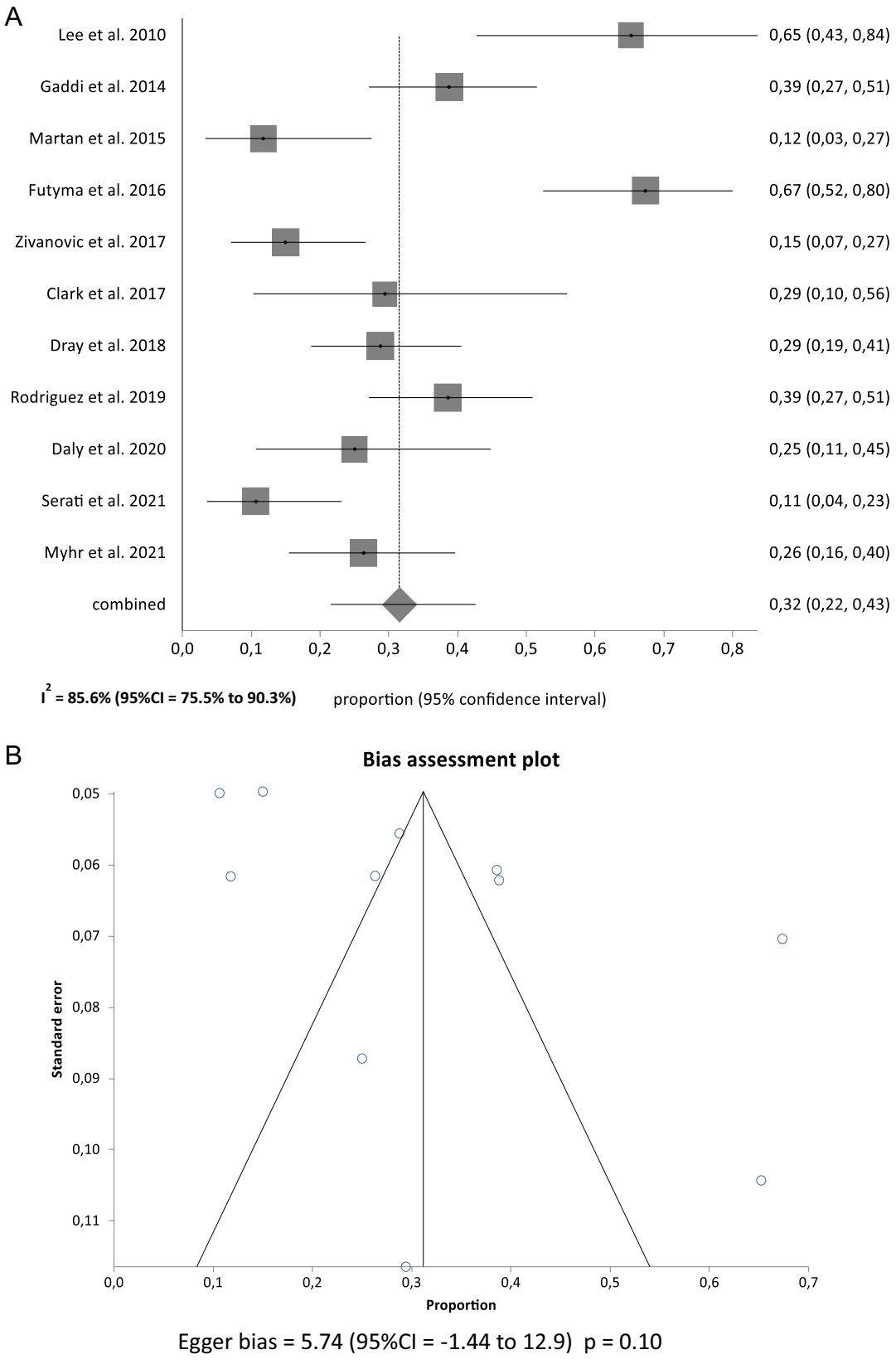
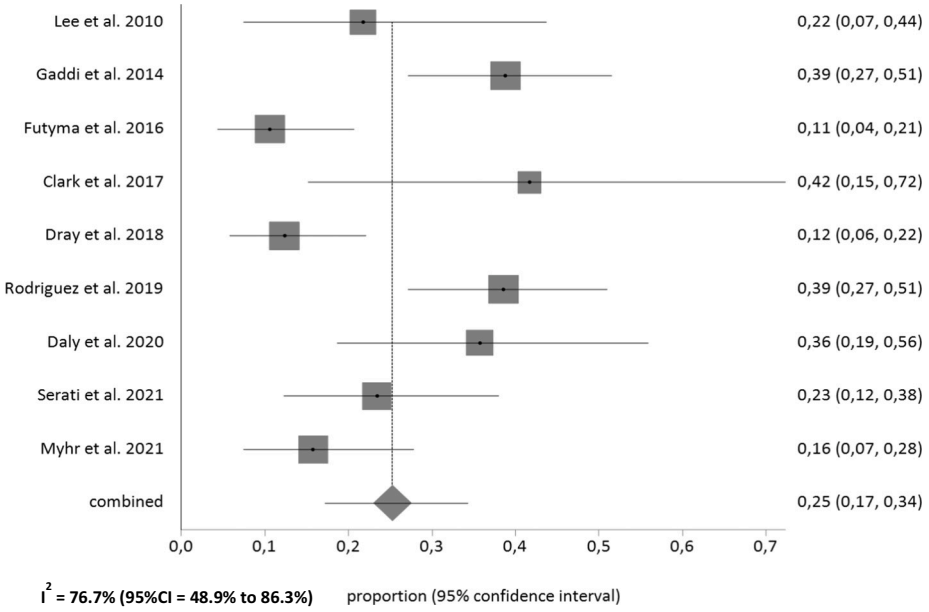


Fig. 4. a. Failure rate (proportion meta-analysis plot - random effect)
b. Failure rate (Bias assessment plot).



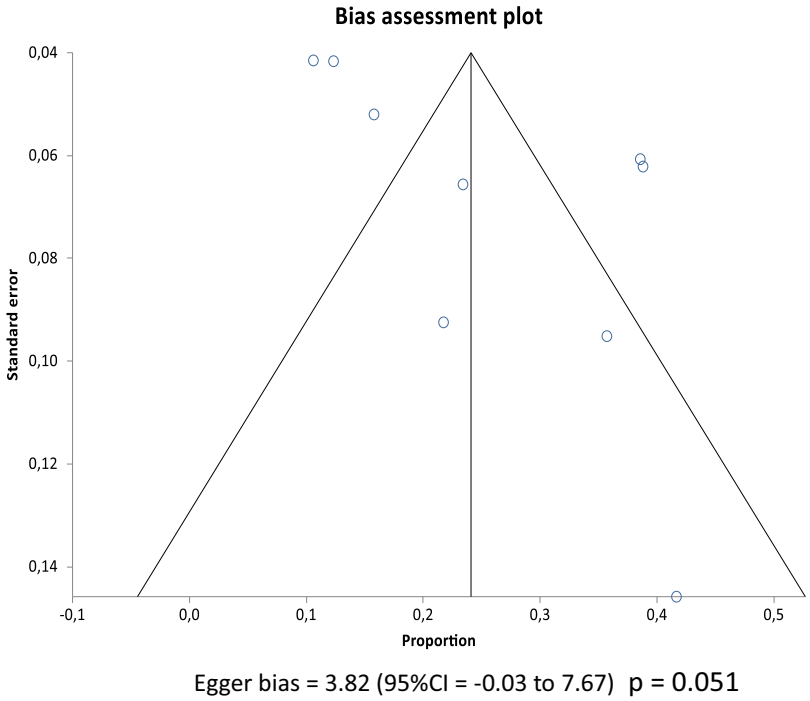


Fig. 5. a. Reoperation rate (proportion meta-analysis plot - random effect)
b. Failure rate (Bias assessment plot).

Table 4
Subgroup meta-analysis.

Bulking agent	Cure and Improvement rate	Failure rate	Re-operation rate
Macroplastique	0.84 (95%CI: 0.77–0.90) $I^2 = 0\%$	0.40 (95%CI: 0.19–0.63) $I^2 = 80\%$	0.31 (95%CI: 0.20–0.43) $I^2 = 33\%$
.			
Bulkamid	0.80 (95%CI: 0.74–0.85) $I^2 = 5\%$	0.20 (95%CI: 0.14–0.26) $I^2 = 14\%$	0.24 (95%CI: 0.13–0.37) $I^2 = 46\%$

and common protocols are needed in order to recommend the use of UBAs for the treatment of more complicated patients. Nevertheless, in this era where the use of MUSs is widely questioned, UBAs could be an effective and safe option for the treatment of rSUI.

Contributors

Andrea Braga contributed to protocol/project development, data collection, statistical analysis, and manuscript writing.

Giorgio Caccia contributed to critical revision.

Andrea Papadia contributed to critical revision.

Giorgio Treglia contributed to statistical analysis and critical revision.

Fabiana Castronovo contributed to data collection.
Stefano Salvatore contributed to critical revision.
Marco Torella contributed to critical revision.
Fabio Ghezzi contributed to critical revision.
Maurizio Serati contributed to critical revision.

Funding

No funding from an external source was received for the preparation of this review.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Declaration of competing interest

The authors declare that they have no competing interest.

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