НИРКИ KIDNEYS

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Effectiveness of bulking agents in managing stress and mixed urinary incontinence: a systematic review and meta-analysis

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Abstract. *Stress urinary incontinence and stress-predominant mixed urinary incontinence are prevalent conditions that significantly impair quality of life, particularly among women. Urethral bulking agents have emerged as a non-surgical treatment option for patients who are hesitant to undergo surgical interventions. The aim of this systematic review and meta-analysis is to evaluate the efficacy and safety of various urethral bulking agents, specifically Bulkamid, Macroplastique, and Urolastic, in treating stress urinary incontinence and stress-predominant mixed urinary incontinence. The review encompasses 15 studies, including randomized controlled trials and cohort studies, with a total of 1,120 patients. The analysis focuses on cure and improvement rates, complications, and the risk of bias associated with the included studies. The findings indicate that bulking agents demonstrate cure and improvement rates ranging from 70 to 80 %, with a pooled average of 75 %. Subgroup analyses reveal cure rates of 76 % for Bulkamid, 73 % for Urolastic, and 77 % for Macroplastique. Despite significant statistical heterogeneity, particularly for Bulkamid and Urolastic, the results suggest that these agents can serve as effective non-surgical options. The outcomes appear consistent across all continents included in this study, reinforcing their potential as reliable alternative globally. However, the review highlights the necessity for well-designed randomized controlled trials to further assess the long-term efficacy and safety of these treatments, ultimately aiming to optimize patient outcomes.*

Keywords: *stress urinary incontinence; mixed urinary incontinence; urethral bulking agents; efficacy; safety; cure rates*

Introduction

Stress urinary incontinence (SUI), characterized by the involuntary leakage of urine during activities such as physical exertions, coughing, sneezing, or laughing, stands as the most prevalent type of incontinence (48 %) [1]. It affects millions of people globally, with approximately 1 in 3 women experiencing symptoms during their lives. This condition occurs when the closure mechanism is unable to handle the sudden increase in bladder pressure, leading to urine leakage through the urethra. Contributing factors include weakened pelvic muscle, thinning of mucous membranes due to postmenopausal estrogen deficiency, and relaxation of urethral ligaments [2].

Studies indicate that SUI significantly impairs people's quality of life, causing emotional distress, social limitations, and a lower quality of life. Up to 70 % of people with SUI avoid social activities such as family gatherings or outings with friends due to fear of leakage, highlighting the condition's significant impact [3].

SUI has various treatment options, ranging from surgical procedures to behavioral therapy and pelvic floor exercise. Among these options, urethral bulking agents has been a less invasive choice for individuals preferring conservative management. Urethral bulking is an FDA-approved treatment for adult women with stress urinary incontinence caused by intrinsic sphincter deficiency. The procedure involves injecting a bulking agent either transurethrally or periurethrally to enhance the urethral closure mechanism, improving urinary control [4]. This therapy has been used for nearly a century, involves injection of bulking agents into

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the submucosal tissues of the urethra, facilitating the restoration of proper closure [5]. SUI is primarily a structural and sphincter-related issue, tissue bulking can offer significant relief by restoring the mucosal seal mechanism. The introduction of injectable bulking agents has provided an additional treatment option for SUI. These agents are favored for their simple outpatient application and favorable safety profile, even for patients with severe health conditions. The most common side effects include pain during injection, and immediate post-procedure complications such as urinary retention and voiding dysfunction, which can be managed with intermittent self-catheterization [6].

Increasingly, women are choosing to have urethral bulking injections as a treatment for SUI. This decision is influenced by patient preference, developments in technology, and the comparative advantages over other treatments. Patients often prefer therapies that disrupt less of their daily routine, which makes urethral bulking agents appealing because they have shorter recovery times and are less invasive. Additionally, technological advancements have led to the development of bulking agents that offer improved efficacy and safety. However, urethral bulking agents should not be seen as a replacement for mid-urethral slings (MUS) in the treatment of female SUI. Instead, they should be regarded as a legitimate alternative for specific subgroups of women with SUI, including elderly patients, those with significant comorbidities who require a low-risk procedure, and younger women who may be considering pregnancy [7].

However, ongoing discussions among the medical community persist about the efficacy and safety of urethral bulking agents, despite their various advantages. The primary topics of discussion include the effects in therapies, variability in patient responses, and risk of adverse events associated with certain agents. Concerns have been raised about how long bulking agents relieve symptoms and the risk associated with the materials used [8]. A study by Lemmon indicates that performing peri-urethral bulking alongside pelvic floor repair results in improved urinary symptoms, with outcomes comparable to those of bulking procedures for SUI alone. Our findings also support that combining bulking with pelvic floor repair is a safe procedure, with transient voiding dysfunction being the most common side effect, which can typically be managed with standard conservative treatments [9]. Furthermore, ongoing discussion addresses the effectiveness of therapy over the long term, the differences in how patients react to different agents, and the occurrence of specific adverse effects such as infections or allergic response [10].

Evidence-based guidance is crucial to assist patients in receiving suitable and effective treatments while reducing risks and complications. Evidence-based methods guarantee the general quality score, safety of the patients, and efficacy of the therapy.Therefore to address this need, we carried out a systematic review and meta analysis. Our study compared the efficacy and safety of various periurethral bulking agent therapies like Macroplastique, Bulkamid, and Urolastic for patients with stress urinary incontinence or mixed urinary incontinence (MUI) with predominant stress. To provide medical experts with useful information on the long-term effects and efficacy of various bulking agents, which will facilitate decision-making and optimize treatment plans to improve patient outcomes and standard of care.

Literature review

Brosche conducted a study on the use of Bulkamid in women with SUI [11]. Their findings indicated high patient satisfaction, with the primary advantage being the ease of administration and shorter recovery periods compared to surgical alternatives. Similarly, Tan introduced MUS, which provided a point of comparison between surgical options and non-surgical treatments like bulking agents. While MUS demonstrated long-term efficacy, the study highlighted the need for non-invasive alternatives such as bulking agents, especially for patients with contraindications for surgery [12].

Fleischmann focused on the use periurethral bulking agents in elderly women who had failed previous sling surgeries [13]. Their analysis showed that bulking agents could serve as a second-line treatment with moderate success rates and manageable complications. Sebesta compared Macroplastique to other agents in a retrospective short study [14]. They supported Macroplastique as a durable solution with fewer complications, though they also acknowledged that follow-up injections were sometimes necessary to maintain efficacy.

In a different approach [5] conducted a randomized controlled trial (RCT) to evaluate the long-term outcomes of Urolastic in treating mixed urinary incontinence. While effective for up to two years post-injection, their study observed a decline in efficacy beyond that period, underscoring the potential need for additional treatments [15] reviewed novel bulking agents, including autologous fat and platelet-rich plasma (PRP). Though still experimental, these agents showed promising results in initial trials and may represent future directions in bulking agent therapy.

Lemmon examined complication rates across different bulking agents, finding that Bulkamid had the lowest rate of complications [9]. In contrast, collagen-based agents were associated with a higher risk of allergic reactions, pointing to the importance of selecting the most appropriate material based on the patient's medical history. Lord added to the discussion by exploring the cost-effectiveness of urethral bulking agents versus surgical options. While bulking agents often require repeat procedures, their analysis showed that they can be more cost-effective in the short term due to reduced hospitalization and quicker recovery times [16].

Patient-reported outcomes also play a significant role in evaluating treatment option. Serati studied how urethral bulking agents impacted quality of life [17]. Their findings indicated that patients who received Bulkamid reported the highest levels of satisfaction and were most likely to recommend the procedure to others. Lastly, a Cochrane review by [18] provided a comprehensive analysis of various interventions for treating SUI. The review concluded that while bulking agents may not be as effective as surgical options, they remain a valuable alternative for patients who prefer non-invasive treatments or who are not ideal candidates for surgery.

Methods

The research protocol was registered in PROSPERO and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Meta-analysis was performed using R-Studio, ensuring methodological rigor and reliability.

Eligibility criteria

Our analysis encompassed studies examining the effectiveness (both subjective and objective) of various urethral bulking agents in treating female stress urinary incontinence or mixed urinary incontinence with a predominant stress component, regardless of prior surgery. We considered RCTs as well as observational prospective or retrospective cohort studies to be appropriate epidemiological designs. Excluded from our review were review articles, case reports, commentaries, editorials, and meeting abstracts. Additionally, we limited inclusion to studies published in English within the past 10 years.

Source

We utilized PubMed, Cochrane, Springer, Scopus, and ClinicalTrials.gov as the search engines for accessing study resources.

Search strategy

The literature search involved using the terms either separately or in combination, as follows:

a) "bulking agent" or "bulking agents"; and

b) "periurethral injection" or "transurethral injection"; and

c) "stress urinary incontinence" or " due to persistent stress urinary incontinence" or "incontinence urinary mixed with predominant stress"; and

d) "woman" or "female".

All relevant articles were meticulously reviewed with lists references evaluated to uncover additional relevant article.

Process of selection

Conducting a narrative synthesis and qualitative analysis. Each researcher independently selected articles based on their titles and abstracts, excluding any that were unrelated. Any disagreements were resolved through discussion among all researchers. if several equal identified with research publication then utilized the data of largest sample. Subsequently, potential reseach evaluated in full-text to sum up the quantitative and qualitative analyses.

Collection of data

Using structured table to extract essential data each eligible study, encompassing authors' names, publication year, study design, bulking agent type, prior surgeries, patient age, body mass index (BMI), menopausal status, parity, type of incontinence, objective and subjective assessment methods, cure and improvement rates, failure level, complications, and follow-up duration in months.

Data

— Subjective assessments are assessed from validated surveys and self-reports.

— Objective assessment using a variety of tests from cough, valsalva, dressing and bladder history.

— The level of improvement was evaluated through self-report as well as the need for and additional incontinence related interventions.

— Failure rates were assessed based on validated questionnaires, cough tests and pad tests

— Complication rates were assessed by employing either the Clavien-Dindo classification or by identifying significant complications associated with stress urinary incontinence.

Results

Initially identified 342 records through various search engines up to the year 2023. After removing 31 duplicates, we screened a total of 311 records. Of these, 256 records were excluded during the screening process, leaving 55 records for further retrieval. Unfortunately, full articles were not found for 17 of these records, resulting in 38 records available for eligibility assessment. Subsequently, 17 records were excluded due to no full-text available. Consequently,

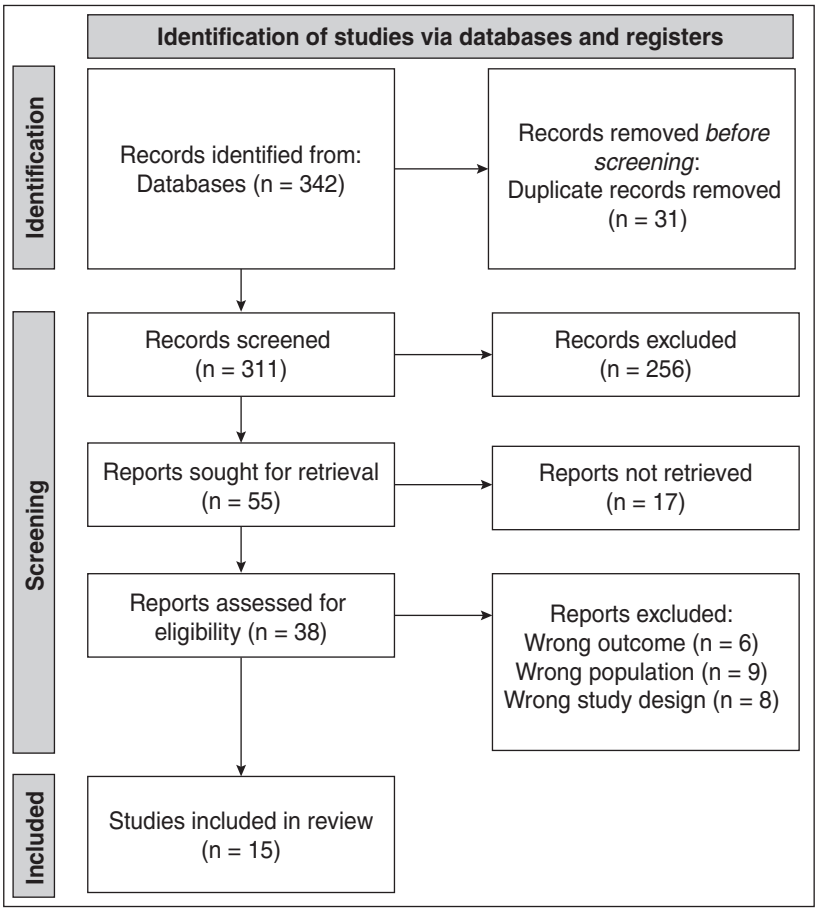

Figure 1. Identification of studies via databases and registers

38 records with full texts were assessed for eligibility and leading to the exclusion of 23 records based on wrong outcomes, populations, or study designs. The remaining 15 studies fulfilled the inclusion criteria and were included in this review.

Study characteristics

We included nine retrospective and six prospective studies. Retrospective studies examine prior data, while prospective studies follow individuals over time to assess UBA effectiveness and results. Table 1 details the study design and patient characteristics. About 11 of 15 studies were monocenter, meaning they were conducted at one medical center. Four multicenter studies showed collaboration between medical centers. This suggests that the majority of research took place at specific institutions rather than spanning multiple sites. This research was done in North America, Europe, Taiwan, and Australia. This international representation is crucial for gaining insights into the utilization of urinary bulking agents across diverse healthcare systems and populations.

The study used several bulking agents. 716 patients (51.3 %) received Bulkamid, followed by Macroplastique with 265 patients (18.98 %), Urolastic with 139 patients (9.96 %), Collagen with 35 patients (2.51 %), Contigen with 33 patients (2.36 %), Coaptite with 27 patients (1.93 %), and PRP with 20 patients (1.43 %). In 161 patients (11.53 %), the proportion of patients who received Bulkamid or Macroplastique is unclear. The study of various materials in treating urine incontinence enriches therapeutic options. Four of the studies included women with major SUI and MUI, whereas the other eleven focused on pure SUI. Participants averaged 61.7 years old and ranged from 41 to 71.7. Five studies provided data on menopause status, ranging from 23.9 to 92.8 %. Menopause due to hormonal changes, can have an impact on bladder function and urinary health. In the studies, the number of pregnancies varied from 1 to 3. Childbirth can weaken pelvic floor muscles, leading to urine incontinence. In addition, the mean BMI of individuals ranged from 22.7 to 30.89 kg/m^2. Bladder and pelvic floor strain, obesity, and a higher BMI can all increase the risk of urine incontinence.

The outcomes of the studies are listed in Table 2. Eleven out of fifteen studies (73.33 %) report UBA cure rates. 13 studies (86.67 %) reported cure and improvement rates, while 7 (46.67 %) reported failure rates. The average follow-up duration was 26.87 months, ranging from 4 to 84. All studies used subjective assessment methods. 11 out of 15 studies (73.33 %) used validated urinary incontinence questionnaires. Three studies (23.8 %) used validated quality-of-life (QoL) questionnaires. Two studies (9.52 %) used self-reported symptoms. Ten of 15 studies (6.67 %) used objective assessment. Seven out of 15 studies (46.67 %) used the pad

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

Author	Year	Sample size (N)	Study design	Mono/ Multi-center	Country	Bulking agent	Type of UI	Mean age (range) ± SD	Menopause (%)	Parity (range) ± SD	Mean BMI (range) ± SD
1	2	3	4	5	6	7	8	9	10	11	12
Gaddi et al.	2014	67	Retrospective	Monocenter	USA	Macroplastique Contigen Coaptite	SUI	62.30 ± 13.85	23.9 (16)	–	28.10 ± 5.73
Pai and Al-Singary	2015	256	Retrospective	Monocenter	UK	Bulkamid	SUI/ MUI	59.8 (31–93)	–	2 (0–4)	27.6 (19.5–47)
Futyma et al.	2015	105	Retrospective	Multicenter	Poland	Urolastic	SUI/ RSUI	63.62 ± 10.11	–	3 (0–6)	30.27 ± 3.27
Rosenfeld et al.	2015	59	Prospective	Monocenter	USA	Macroplastique	SUI	65.80 ± 9.74	–	2.25 ± 1.19	27.29 ± 10.09
De Vries et al.	2017	34	Retrospective	Multicenter	Netherlands	Urolastic	SUI	64.5 (23.3–89.9)	–	–	–
Zivanovic et al.	2017	55	Prospective	Monocenter	Switzerland	Bulkamid	SUI/ MUI	71.7 ± 10.7	–	–	28.8 ± 3.9
Clark and Welk	2017	17	Retrospective	Monocenter	Canada	Bulkamid	SUI/ MUI	70 (59–78)	–	–	–
Dray et al.	2018	73	Retrospective	Monocenter	USA	Macroplastique (38) Collagen (35)	SUI	65.1 ± 12.6	–	–	30.1 ± 7.1

End of Table 1

1	2	3	4	5	6	7	8	9	10	11	12
Rodríguez et al.	2020	70	Prospective	Monocenter	USA	Macroplastique	SUI	62.7 ± 10.7	92.8 (65)	2.4 ± 1.2	27.2 ± 5.9
Daly et al.	2020	114	Retrospective	Monocenter	Scotland	Macroplastique Bulkamid	SUI	60	–	–	30.89

Table 2. Included studies' outcome measures in the systematic review and meta-analysis

Author	Year	Cure rate, % (N)	Cure and improvement rate, % (N)	Failure rate, % (N)	Complication rate, % (N)	Follow-up (months)	Subjective assessment	Objective assessment	Complication
1	2	3	4	5	6	7	8	9	10
Gaddi et al.	2014	61.2 (41/67) (S + O)	79 (53/67)	38.8 (26/67)	2.98 (2/67)	12	Self-report improvement	Cough test	Transient urinary retention
Pai et al.	2015	42.9 (110/256) (S)	82.8 (212/256) (S)	–	0 (0/256)	60	ICIQ-UI SF VAS	24-hour pad test	No complications
Futyma et al.	2015	45.7 (48/105) (O)	60.9 (64/105)	–	17 (17/105)	12	Stamey	Pad test	Bladder outlet obstruction Displacement bulking material Recurrent urinary tract infection
Rosenfeld et al.	2015	5.08 (3/59) (O)	74.6 (44/59) (S)	25.42 (15/59)	–	9	UDI-6 VAS	Pad test	–
De Vries et al.	2017	–	85.3 (29/34) (S)	–	65.71 (23/35)	12	PGI-I Clavien-Dindo complications	–	Clavien-Dindo complications I–IIIB
Zivanovic et al.	2017	25.4 (14/55) (S + O)	83.6 (46/55)	16.4 (9/55)	29 (16/55)	12	VAS	Cough test Pad test 3-day micturition diary 1-hour pad test	Persistent urge urinary incontinence Voiding dysfunction UTI *De novo* urgency
Clark et al.	2017	–	71 (12/17)	29.4 (5/17)	–	12	ICIQ-UI	–	–
Dray et al.	2018	24.7 (18/73) (S + O)	71.3 (52/73)	28.8 (21/73)	–	4	AUAS index M-ISI index	Pad test	–
Rodríguez et al.	2020	69 (48/70) (S + O)	83 (58/70)	31 (22/70)	0 (0/70)	46	UDI-6 QoL	Pad test	No complications

End of Table 2

1	2	3	4	5	6	7	8	9	10
Daly et al.	2020	–	60.5 (69/114) (S)	–	16.7 (19/114)	56	Patient reported outcomes scale ICIQ-UI SF	–	Post voiding dysfunction Urinary tract infection Transient urethral pain
Brosche et al.	2021	16 (62/388) (S + O)	65.2 (253/388)	–	37.6 (118/388)	84	ICIQ-UI SF VAS QoL Complications	Pad usage	Urinary tract infection Transient prolonged emptying time Nocturia Residual urine > 50 ml/s Persistent disuria Frequent urination
Long et al.	2021	20 (4/20) (S)	80 (16/20) (S)	–	0 (0/20)	6	ICIQ-UI SF UDI-6 IIQ-7 OABSS POPDI-6	–	No complications
Ghoniem et al.	2021	–	70 (49/70) (S)	–	12.8 (8/70)	36	I-QOL PGI-S Stamey	–	Transient disuria Hematuria Pain at injection site Urinary tract infection
Serati et al.	2021	81 (38/47) (S) 83 (39/47) (O)	–	19 (9/47)	8.5 (4/47)	36	ICIQ-UI SF PGI-I UDI-6	Negative stress test	Clavien-Dindo complications I–II
Serati et al.	2023	80.9 (17/21) (S) 76 (16/21) (O)	–	–	14.2 (3/21)	6	PGI-I Clavien-Dindo complications FSFI	Negative stress test	Clavien-Dindo complications I–II

Notes: (S) — subjective cure rate; (O) — objective cure rate; VAS — Visual Analogue Scale; I-QOL — Incontinence Quality of Life; 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; PGI-I — Patient Global Impression — Improvement; SI — stress incontinence; UI — urinary incontinence; OABSS — Overactive Bladder Symptom Score; POPDI — Pelvic Organ Prolapse Distress Inventory; IIQ — Incontinence Impact Questionnaire.

test, while 4 out of 15 studies (26.67 %) used the cough or Valsalva stress test. One study (6.67 %) used micturition diaries. The study employed diverse results, methodologies, and follow-up durations.

Risk of bias assessment

Several studies [9, 18–25] presented a low risk of bias (RoB) with total quality scores of 7 out of 9. The results of all of the other studies [11, 26–31] showed that the RoB was moderate to high. Specifically, four of the studies received a score of six out of nine, two received a score of five out of nine, and one received a score of four out of nine.

The lack of case representativeness was the main contributing cause of bias in this study, with one article having a high RoB and six articles with moderate RoB. Furthermore, none of the studies included the control selection, which indicates a possible source of bias. Out of fifteen studies, eight studies showed a low RoB in the ascertainment of exposure. The majority of the studies also had adequate outcomes and follow-up evaluations, which improved the research's overall reliability.

Synthesis result

The related I^2 test result was 77 % (95% CI: 62–86 %), demonstrating significant statistical heterogeneity among

the studies. The overall cure and improvement rate ranged from 70 to 80 % in the included studies with a pooled value of 75 %. Besides, the risk of publication bias was not found through a visual analysis of the funnel plot and the Egger's test, which produced a result of 0.47 (95% CI: –2.21 to 3.14; p = 0.74).

We performed a subgroup analysis of the three most common bulking agents used which are Bulkamid, Urolastic and Macroplastique. The pooled cure and improvement rate was 76 % (95% CI: 66–86 %), 73 % (95% CI: 49–97 %) and 77% (95% CI: 70–84 %) for Bulkamid, Urolastic and Macroplastique, respectively. We find significant heterogeneity in all the group except Macroplastique group Bulkamid (I^2 = 90 %), Urolastic (I^2 = 90 %), Macroplastique (I^2 = 19 %).

Another subgroup analysis was conducted based on the continents where bulking agents were used. The pooled rates of cure and improvement were 74 % (95% CI: 71–81 %) for the American, 75 % (95% CI: 67–83 %) for European, and 80 % (95% CI: 56–94 %) for Asian. Significant heterogeneity was observed in all groups except for the American, with I^2 values of 0.4 % for the American, 87 % for Europe, and 76.6 % for Asian.

Researchers evaluate in three categories: low RoB (7–9 stars), moderate RoB (5–6 stars), and high RoB (less than 5 stars).

Discussion

This study offers insight into the efficacy and safety of bulking agents in treating SUI and stress-predominant MUI. Using a systematic review and meta-analysis approach, we collected data from a variety of studies, including randomized controlled trials, cohort studies, and retrospective analyses. Our study aims to evaluate the cure and improvement rates of bulking agents with various follow-up durations, assess the risk of bias, and look at the side effects and complications that arise. While previous studies, such as Braga's meta-analysis, focused on specific populations, Our study included a more broader population of women, including those who were suffering SUI for the first time or had previously undergone surgical intervention for SUI [17].

There are various types of bulking agents, with several commonly utilized in this research, including Bulkamid, Macroplastique, and Urolastic. Furthermore, autologous platelet-rich plasma stands as another potential option as a bulking agent, as shown by a study conducted by Long [30]. Bulking agents are administered either periurethral or transurethrally into the submucosa. They enhance the closure of the urethra during the storage phase of the micturition cycle and periods of elevated abdominal pressure. They play a role in improving urinary incontinence through their mass effect, which increases muscle fiber length and strengthens the urethral sphincter.

Bulkamid is among the most commonly used bulking agents. According to research by Brosche, involving 388 participants, cure and improvement rates stood at 67.1 % seven years after the initial injection. Remarkably, even when used as a secondary therapy subsequent to prior treatments for SUI or stress-predominant MUI, the majority of patients reported sustained long-term benefits [11]. Another frequently administered bulking agent is Macroplastique. In studies conducted by Rodríguez et al., findings revealed that among 70 women diagnosed with confirmed SUI, 83 % achieved a subjective improvement rate after follow-up of nearly 4 years. This study suggests that Macroplastique injection is a durable and effective management option for SUI, although a second injection may be required to achieve the desired success.

Another viable option among bulking agents is Urolastic. In a study conducted by de Vries et al., it was found that 88 % of patients treated at the general hospital reported subjective improvement at a median follow-up of 12 months. The rate of complications, classified as Clavien-Dindo > 2,

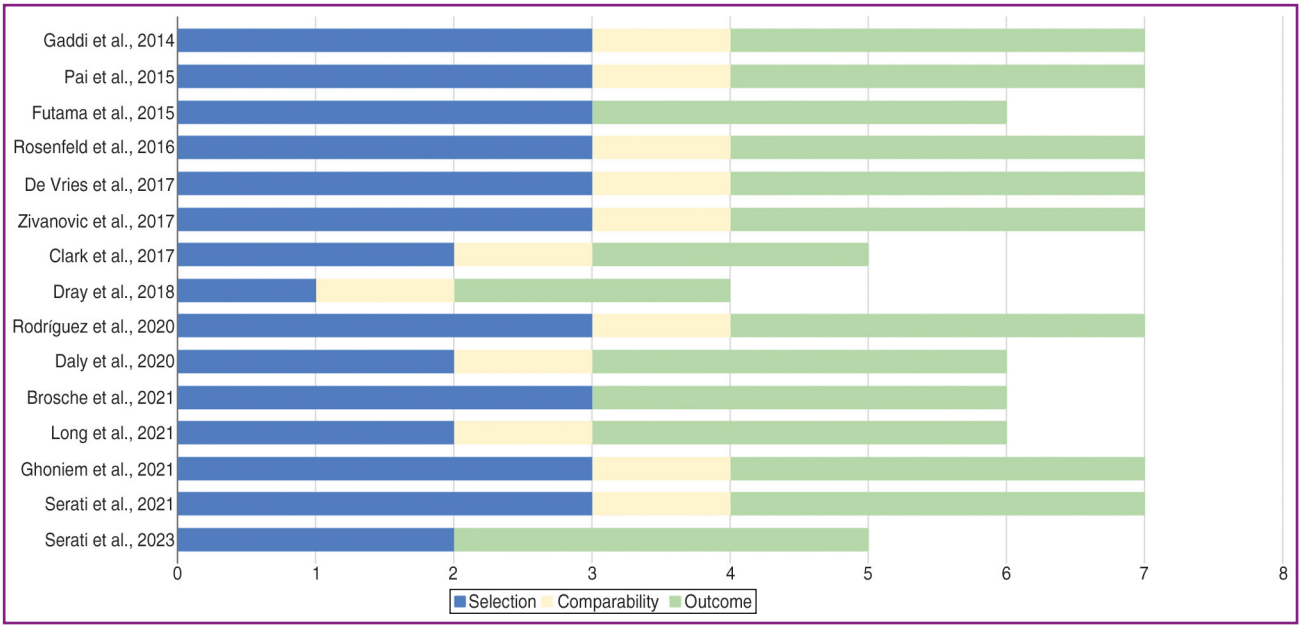

Figure 2. A comprehensive Newcastle-Ottawa scale of each included cohort study

Table 3. A comprehensive 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	
Gaddi et al., 2014	★	0	★	★	★	0	★	★	★	7★
Pai et al., 2015	★	0	★	★	★	0	★	★	★	7★
Futyma et al., 2015	★	0	★	★	0	0	★	★	★	6★
Rosenfeld et al., 2016	★	0	★	★	★	0	★	★	★	7★
De Vries et al., 2017	★	0	★	★	★	0	★	★	★	7★
Zivanovic et al., 2017	★	0	★	★	★	0	★	★	★	7★
Clark et al., 2017	0	0	★	★	★	0	★	★	0	5★

stood at 24 %. Notably, despite the occurrence of complications, the implantation of Urolastic appears to be a safe procedure, characterized by the absence of migration or undesired tissue reactions [22].

Our meta-analysis revealed cure and improvement rates ranging from 70 to 80 % across involved studies with combined 75 % rate. We also conducted subgroup analyses by geographic region, categorized by continent. Bulking agents are predominantly utilized in Western regions, such as the Americas and Europe, with only one study in this research originating from Asia. Research on the use of urethral bulking agents in Asia is relatively scarce, with most studies primarily conducted in Western regions. Despite this regional distribution, analysis reveals that the treatment outcomes for bulking agents are consistent across the three continents, with cure and improvement rates of approximately 75 % in Asia and Europe and 76 % in the Americas.

However, heterogeneity between studies, variations in methodology, duration of follow-up, and inclusion of studies with moderate or high risk of bias may have influenced the overall findings. Study heterogeneity is a key concept for interpreting meta-analysis results. While results from multiple studies often vary, studies are considered heterogeneous when their core target outcomes differ. Heterogeneity may arise due to variations in study design or data, such as differences in target populations, intervention doses, timing of outcome measurements, recruitment and survey methods, measurement tools, or analytical approaches, including how covariates are adjusted [32].

Clinical and methodological heterogeneity can be managed by restricting criteria during the planning phase and carefully selecting eligible studies. Subgroup analysis, which is pre-specified in the protocol, is one approach to addressing heterogeneity, while meta-regression can also be used to identify and explain variability. However, both subgroup analysis and meta-regression are only applicable to known or potential sources of heterogeneity. Importantly, the presence of heterogeneity does not render a meta-analysis unnecessary or ineffective. Some experts argue that heterogeneity is an inherent aspect of meta-analysis, as it aims to integrate findings from studies conducted in diverse settings [33].

In the term of safety and efficacy, a study by Campanella suggests that Single Incision Slings (SIS) and Urethral Bulking Agents (UBA) are comparable in terms of both effectiveness and safety for treating SUI. The key distinction was the absence of groin pain following UBA treatment. Over a 29-month follow-up, bulking agents demonstrated promising efficacy and safety, with treated patients experiencing fewer postoperative complications. Additionally, there was no significant difference in quality of life or sexual activity between patients receiving SIS or UBA. This makes bulking agents a reliable treatment option when appropriate patient selection is made [34].

These findings highlight the importance of bulking agents as an effective non-surgical treatment option for women with SUI or stress-predominant mixed urinary incontinence. For example, patients who are hesitant about undergoing surgery or experiencing adverse effects from treatment may find bulking agents attractive, thereby improving quality of life and treatment satisfaction. Future research should prioritize conducting well-designed randomized controlled

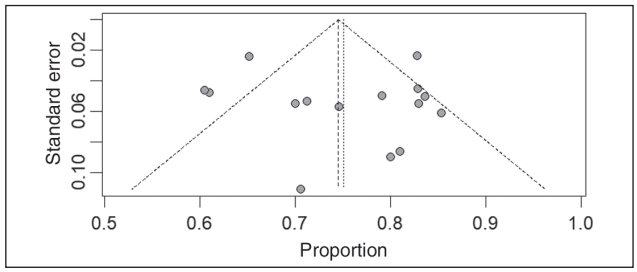

Figure 3

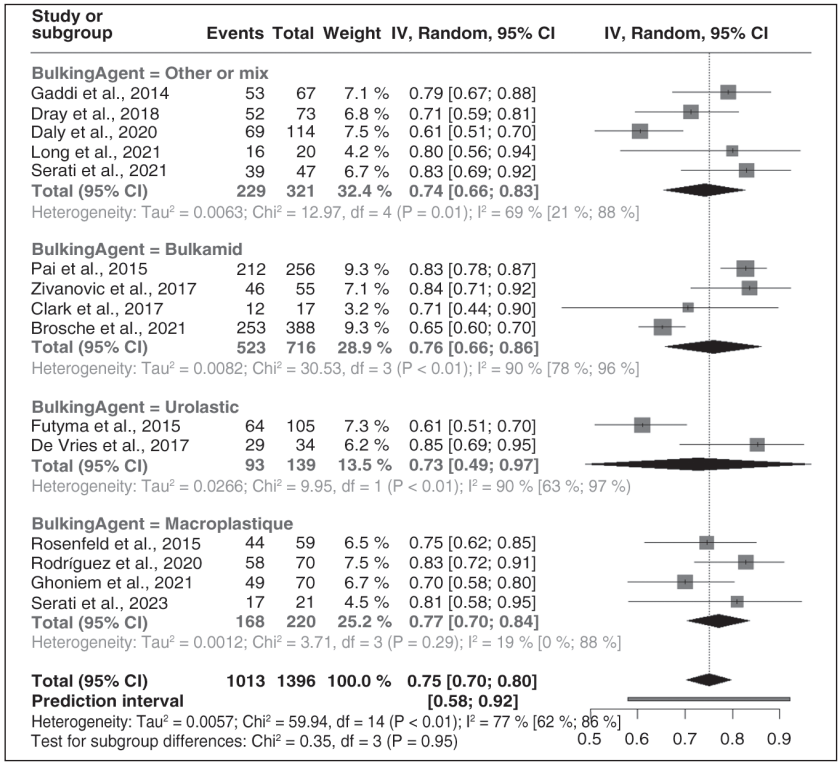

Figure 4

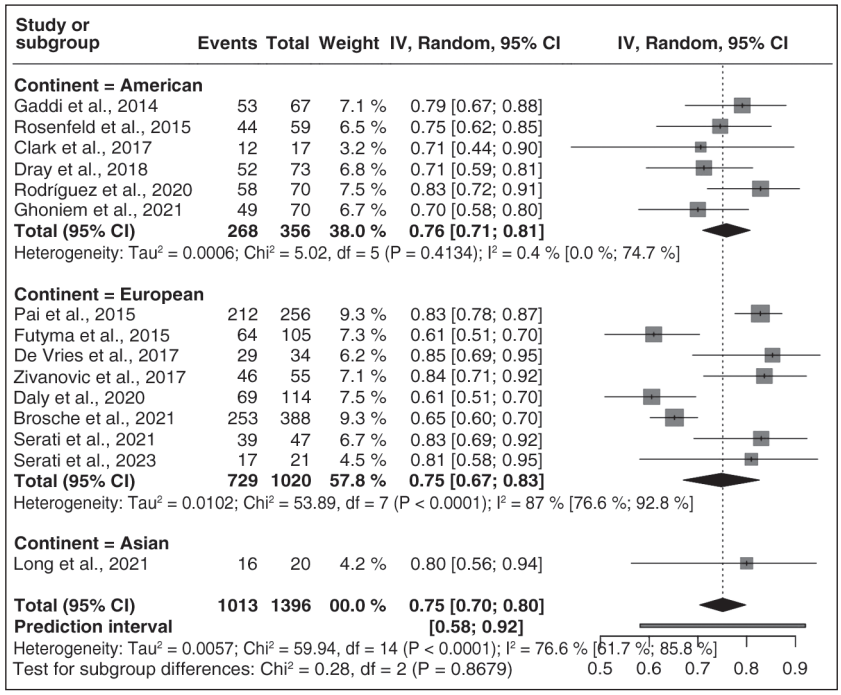

Figure 5

trials to rigorously assess the efficacy and safety of bulking agents, allow better comparison of outcomes, and establish more reliable treatment guidelines.

Suggestion

Our study demonstrated a considerable degree of heterogeneity. Therefore, we recommend that future research adopt more standardized protocols, particularly in studies involving the bulking agents Bulkamid and Urolastic. Additionally, further research on the effectiveness and safety of bulking agent therapy for treating stress and mixed urinary incontinence is warranted to enhance the reliability of clinical data.

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Ефективність наповнювачів у боротьбі зі стресовим і змішаним нетриманням сечі: систематичний огляд та метааналіз

Резюме. Стресове нетримання сечі й змішане нетримання сечі з переважанням стресового компонента є поширеними станами, що значно погіршують якість життя, особливо серед жінок. Уретральні наповнювачі з'явилися як варіант нехірургічного лікування пацієнтів, які вагаються щодо оперативного втручання. Метою цього систематичного огляду та метааналізу є оцінка ефективності й безпеки різних наповнювачів уретри, зокрема Bulkamid, Macroplastique і Urolastic, у лікуванні стресового нетримання сечі та змішаного нетримання сечі з переважанням стресового компонента. Огляд охоплює 15 досліджень, включно з рандомізованими контрольованими й когортними дослідженнями, із загальною кількістю 1120 пацієнтів. Автори зосереджуються на показниках одужання й покращення стану пацієнтів, ускладненнях і ризику системної помилки. За результатами дослідження, показники одужання й покращення коливаються в діапазоні від 70 до 80 %, із зведеним середнім 75 %. Аналіз по підгрупах виявив, що показники одужання становили 76 % для Bulkamid, 73 % для Urolastic і 77 % для Macroplastique. Незважаючи на значну статистичну неоднорідність, зокрема для Bulkamid та Urolastic, результати свідчать про те, що ці засоби можуть бути ефективними нехірургічними варіантами. Проте в огляді підкреслюється необхідність проведення добре спланованих рандомізованих контрольованих досліджень для подальшої оцінки довгострокової ефективності й безпеки цих методів з метою оптимізації результатів лікування пацієнтів.

Ключові слова: стресове нетримання сечі; змішане нетримання сечі; наповнювачі уретри; ефективність; безпека; курси лікування