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Periurethral injection therapy in women with stress incontinence

CLINICAL REVIEW

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Periurethral injection offers an alternative to the current main method for surgical treatment of stress incontinence in women, which is a polypropylene sling that is placed without tension below the mid-urethra. Injection therapy is a simple, gentle method that provides significant improvement in the degree of leakage and quality of life, but the results are not on a par with the polypropylene sling. Injection therapy may be relevant when the main method is not suitable or desired.

Stress incontinence is a widespread disorder among women, and more than 2 000 women undergo surgery for this condition in Norway each year (1). Starting from the 1960s, retropubic colposuspension was the gold standard for surgical treatment of stress incontinence in women, but in the last 20 years, tension-free vaginal tape (TVT) has replaced it as the main method and is now considered the gold standard. More than 95 % of all surgical interventions for incontinence in Norway are currently in the form of tension-free vaginal tape (1). During this intervention, a polypropylene tape is placed as a sling without tension below the mid-urethra. This is a safe operation with good results (2,3). There are many variants of the tension-free tape. The results for the different types of slings currently in use are relatively similar (2,3), and for reasons of simplicity the term 'tension-free vaginal tape' is used for all of them in this clinical review.

Sometimes, however, other methods are called for. Periurethral injection of a bulking agent has been in use for more than one hundred years, and a number of variants have been described (Table 1). In Norway, only polyacrylamide hydrogel is currently used, in a total of eight Norwegian gynaecological departments.

Table 1

Historic overview of periurethral injection techniques

First published	Substance (trade name)
1904	Paraffin[1]
1938	Sodium morrhuate (≈ cod liver oil)[1]
1973	Polytetrafluorethylene (Polytef, Teflon)[2]
1989	Collagen (Contigen)[2]
1989	Autologous fat[3]
1992	Silicone (Macroplastique)[4]
1999	Dextranomer/hyaluronic acid (Zuidex)[2]
1999	Carbon spheres (Durasphere)[4]
2001	Calcium hydroxylapatite (Coaptite)[4]
2003	Ethylene vinyl alcohol (Tegress, Uryx)[2]
2006	Polyacrylamide hydrogel (Bulkamid)
2013	Polydimethylsiloxane (Urolastic)[4]
In the future	Myoblasts, fibroblasts or stem-cell derived cells?

[1]Only of historic interest

[2]Withdrawn from the market

[3]Poor long-term results and may cause fat embolism

[4]Not marketed in Norway

The purpose of this article is to provide a review of polyacrylamide hydrogel. The article is based on the author's clinical experience and a search in Embase and MEDLINE up to February 2018 with a discretionary selection of literature.

Polyacrylamide hydrogel

Polyacrylamide hydrogel (Bulkamid) has been in medical use for more than 30 years as a bulking agent in cosmetic surgery and ophthalmic surgery (5, 6). This substance was approved for medical use in Europe in 2001. The first study of the use of polyacrylamide hydrogel for periurethral injection to treat urinary incontinence in women was started in 2001 and published in 2006 (7).

The hydrogel consists of 2.5 % polyacrylamide and 97.5 % water, and has the appearance of a hydrophilic, transparent jelly. A small volume (0.5–2 ml) is injected under the mucous membrane in the urethral wall through a special urethroscope. This can be done under local anaesthetic, commonly in day surgery. The injection causes minimal tissue reaction.

The substance is integrated into the tissue through the formation of a thin web of connective tissue in the implant, but without thick encapsulation of connecting tissue. The hydrophilic nature of the substance permits aqueous exchange from the surroundings and keeps it soft, and its volume remains unchanged (6). The connective tissue anchors the implant and keeps it from migrating (6). The implant appears to be safe in both the short and long term (5, 8).

Effects of periurethral injection therapy

There are three hypotheses regarding how the urethral continence mechanism is improved with the aid of a periurethral injection: (a) a narrower urethra that closes better ('better gasket'), (b) better pressure transfer, and (c) better muscle contractility because the muscle cells in the urethra are put under tension (9). All these elements are likely to be relevant.

Indications for injection therapy

As of today, periurethral injection has not quite established its place in the treatment hierarchy, but the 2017 report from the International Consultation on Incontinence (2) states the following indications: patients with stress incontinence who are not eligible for tension-free vaginal tape, patients who want a less invasive procedure, and patients who have undergone previous incontinence surgery. In my experience, this is the way the substance is used in Norway. Clinical experience has shown that periurethral injection therapy can be well suited for lighter degrees of leakage, in women with low urethral closure pressure (urethral incompetence) and in women with low urine flow and/or incomplete bladder emptying. Injection therapy has been shown to produce good outcomes also in older women (10) and in women who have undergone radiation therapy (2).

Results from the use of polyacrylamide hydrogel

The last Cochrane report on periurethral injection from 2017 (11) concludes that there is no unequivocal difference in effect between the various injection methods that were assessed, and that the results for injection therapy are better than for conservative treatment, but poorer than for colposuspension. Polyacrylamide hydrogel is not included in this report, but this substance is likely to be at least as effective as other agents used for periurethral injection, and probably safer (12, 13). An American study from 2014 that compared polyacrylamide hydrogel with collagen injection in 345 women found these methods to be of equal value (12), and a recent review article that compared polyacrylamide hydrogel (Bulkamid) with polydimethyloxane (Macroplastique) came to the same conclusion (13). As long as the results for polyacrylamide hydrogel are approximately on a par with those of other injection techniques, we may assume that this substance also fails to measure up to tension-free vaginal tape or colposuspension. It should be noted, however, that injection therapy is used most often as a reserve method when tension-free vaginal tape is deemed undesirable, and results from studies of polyacrylamide hydrogel are therefore not directly comparable to other methods because of their different patient selection. To date, only two studies that directly compare injection therapy with other surgical methods have been published (14, 15). No studies that compare polyacrylamide hydrogel with tension-free vaginal tape or colposuspension have been published.

It is nevertheless generally accepted that injection therapy is a more gentle method with a lower risk of complications than tension-free vaginal tape (8, 11, 14). In contrast to tension-free vaginal tape, injection therapy does not result in any notable obstruction, meaning

that there is less risk of postoperative bladder voiding problems (11). The procedure is quicker and simpler to perform, and the recovery period is short. In practice, more than one or two days of sick leave is rarely necessary.

All published studies on injection with polyacrylamide hydrogel have found statistically significant improvement in the degree of leakage and/or quality of life: 45–86 % of the patients are defined as 'responders' (defined as continent or with more than 50 % improvement, alternatively 'satisfied') and 24–43 % became fully continent with follow-up of up to three years (8, 13, 16).

Only a single study with more than three years' follow-up has been published to date (17). This study had eight years of follow-up and showed that 25 % of the patients were continent at that time, while another 17 % had improved their condition. The King's Health Questionnaire's QoL (Quality of Life) score had fallen from 11 to 2 (i.e. improved quality of life), and 38 % had undergone repeat surgery over the period, either with a further injection or tension-free vaginal tape. Vaginal ultrasound examination showed that the injection deposits were present in all patients (17).

All operations for stress incontinence in women in in Norway must be reported to the Norwegian National Female Incontinence Registry, a national registry with reporting obligation (1). For the years 2014–2016, a total of 6 570 tension-free vaginal tape procedures and 217 polyacrylamide hydrogel injections were reported to the registry (S. Kulseng-Hanssen, personal communication).

An American economics study concluded that polyacrylamide hydrogel is less costly than tension-free vaginal tape in a one-year perspective (18), and the Cochrane report from 2017 concludes that injection therapy with up to two injections is cheaper than tension-free vaginal tape (11).

Complications and disadvantages of using polyacrylamide hydrogel

Periurethral injection therapy entails a clear learning curve. The procedure requires a certain amount of manual dexterity, and doctors who have performed many interventions have the best results (19). This procedure should therefore be restricted to few surgeons in each department that provides this treatment. The results are poorer for higher degrees of incontinence than for lower degrees (19). Moreover, in some cases there is a need for a renewed injection, either because of insufficient primary effect or because the effect has abated. Repeated injections are reported for 12–77 % of the patients, 24 % on average (8). The literature describes a low risk of infection in the implant (6), but the substance is a good growth medium for bacteria, and an infection may be difficult to treat (6, 20). Antibiotic prophylaxis is therefore recommended in association with the intervention, also because injection therapy alone carries a 5–10 % risk of postoperative urinary tract infection (7, 13, 21, 22).

Any surgical intervention against stress incontinence may cause complications such as urinary retention, pain, bleeding, surgical infection and urinary tract infection. De novo urgency incontinence may also occur. The risk of all these complications is lower for injection of polyacrylamide hydrogel than for tension-free vaginal tape (8, 11) and most of the other injection substances (21).

The use of synthetic mesh (polypropylene) in vaginal surgery for genital prolapse has been popular for some time, but its use has been criticised due to a significant risk of complications. The health authorities in Canada, the EU, Scotland and the United States have therefore warned against such use. Tension-free vaginal tape with the use of a polypropylene sling to treat stress incontinence has been determined as safe (22–24), and *no* warnings against the use of this method have been issued. However, doubts about the use

of synthetic fibre mesh in prolapse surgery have spread to the use of tension-free vaginal tape to treat incontinence. For this reason, it is conceivable that demand will increase for other methods, such as periurethral injection.

Future development

New substances for periurethral injection are constantly being developed, and substances that are superior to polyacrylamide hydrogel may come on the market. Moreover, research is being undertaken on various stem cells and muscle cells for periurethral injection therapy, and this may possibly become a form of treatment in the future, but as of today, there is still a long way to go before such treatment becomes available (8).

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