Title: Zuidex™ versus Contigen® for Stress Urinary Incontinence

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Context and policy issues:
Stress urinary incontinence (SUI) is the involuntary leakage of urine during exercise or movements such as coughing, laughing, or sneezing. These activities cause increases in intra-abdominal pressure that lead to involuntary leakage of urine in the absence of bladder contraction. SUI is usually caused by weak or damaged muscles and connective tissues of the pelvic floor, or by weakness of the urethral sphincter itself. SUI patients can be divided into two groups: those with urethral hypermobility and those with intrinsic sphincteric deficiency (ISD) where there is damage to the urethral sphincter arising with prior surgery, spina bifida, or childbirth. An estimated one in three women may experience urinary stress incontinence at some point in their lives. It can happen at any age, although it is more common in women between the ages of 35 and 60. Urinary stress incontinence is rare in men, and is usually a result of injury or prostate surgery. One source states that in the United States, 25 million individuals suffer from SUI (85% are female and 56% are less than 65 years of age). An Ontario survey found that half of the women 45 years old and older who attended two family medicine clinics presented with urinary incontinence. Approximately a third of these reported SUI.

Typically, first-line treatment is conservative and includes lifestyle adjustments to reduce pressure on the bladder (e.g. smoking cessation, weight control, and fluid intake), pelvic floor exercises, electrical stimulation, or biofeedback. If the condition does not improve, surgical options for women include bladder neck suspension, implantation of an artificial sphincter or sacral nerve simulator, tension-free vaginal tape, or traditional suburethral slings. Due to limited evidence of efficacy for medications (including oral/vaginal estrogen in postmenopausal women, imipramine, and duloxetine), surgery is usually recommended over pharmacologic therapy. However, open surgery means hospitalization for a few days and increased risk for serious complications including bleeding; surgical injury; infection; cardiac, thromboembolic, or pulmonary events; and urinary retention.
Periurethral injections of bulking agents offer an alternative to surgery for SUI associated with ISD when lifestyle modifications and pelvic strengthening techniques, or prior surgery fail to adequately control symptoms. Most surgeons no longer use bulking agents for hypermobility-related stress incontinence because of the profusion of new synthetic slings that are more effective and durable. Non-absorbable bulking agents include Macroplastique® (silicone particles), Polytef (polytetrafluoroethylene), DuraspHERE® (carbon-coated beads), and Coaptite® (calcium hydroxyapatite). Absorbable bulking agents include Contigen® (glutaraldehyde cross-linked bovine collagen), Uryx® (ethylene vinyl alcohol copolymer), Zuidex™ (dextranomer/hyaluronic acid), and autologous fat. Bulking agents act to increase tissue bulk around the urethra, thereby increasing resistance to the outflow of urine. Periurethral injection of bulking agents is administered in an outpatient procedure under local anesthesia. Therefore, the procedure is associated with a shorter recovery time and lower risk for complications than surgery. Transient urinary retention, hematuria, sterile abscess formation, irritative voiding symptoms and urinary tract infection are all common treatment-related adverse effects. These usually resolve spontaneously within a few days or with appropriate antibiotic treatment or catheterization.

While autologous fat, Macroplastique, Contigen, DuraspHERE and Polytef have all demonstrated positive short-term results, none have met both criteria for success (remaining efficacious over time) and maintaining a low side-effect profile. Use of Polytef has been limited due to evidence of granuloma formation and migration to other tissues. Macroplastique has also become unpopular due the potential for an autoimmune reaction and possible migration to other organs. Autologous fat is difficult to harvest, is reabsorbed from the injection site at an unacceptably high rate, and has been associated with a rare complication of fat embolization. DuraspHERE beads can be cumbersome to inject and sterile abscess formation has been reported. Although experience with Contigen indicates a good safety profile (there is no evidence the implant causes an inflammatory reaction or granuloma formation, and it is not known to migrate), resorption occurs over time decreasing long-term efficacy and repeat injections are often required. Results from several observational trials of Contigen indicate that early results are generally good with success rates of 72% to 100%. Longer-term results with follow-up of up to 4 years of women who are cured or improved vary from 57% to 94%. While Contigen is currently the most widely used bulking agent, the optimal timing and frequency of injection have not been established. In addition, preoperative allergy testing one month prior to the procedure is necessary since 1-4% of women report skin hypersensitivity.

Zuidex administered via an implacer device is one of the newest bulking agents available for treatment of SUI. It was licensed by Health Canada (classified as a medical device) in 2004. Zuidex is a highly viscous gel of dextranomer microspheres and non-animal stabilized hyaluronic acid. The gel has no immunogenic properties, and has not been shown to migrate to different organs after submucosal injection. The implacer device has been developed to allow reproducible urethral injection by guiding the gel to the appropriate area. As a relatively new treatment, considering the overall impact of
Zuidex in terms of clinical outcome, long-term safety and efficacy, and cost is necessary in order to make a decision regarding implementation. The available evidence for the clinical and cost-effectiveness of Zuidex in comparison to Contigen will be discussed.

**Research questions:**
What is the comparative clinical effectiveness (benefit and harm) and cost-effectiveness of Zuidex and Contigen for urinary stress incontinence?

**Methods:**
A literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 2, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI’s HTAIS database, EuroScan, international HTA agencies, and a limited Internet search. Bibliographies of relevant sources were also scanned to identify further evidence. Results include English language publications from 2002 to date. Links to online full-text references or abstracts are provided where available.

**Summary of findings:**
No health technology assessments were identified, nor were any published, randomized controlled trials found that examine the safety and efficacy of Zuidex in comparison to Contigen or other treatments for SUI (though a multicentre trial is currently underway).

A 2003 Cochrane Collaboration systematic review examined the effects of periurethral injection therapy for the treatment of urinary incontinence in women. Seven randomized and quasi-randomised controlled trials were identified where at least one management arm involved periurethral injection therapy (including autologous fat, Macroplastique, Durasphere, Coaptite, Uryx, and Contigen). No studies could be located that compared periurethral injection to conservative therapy (lifestyle modifications, pelvic floor exercises, electrical stimulation, biofeedback, or pharmacotherapy). No studies examining Zuidex were included. Due to significant heterogeneity in study design and limited available data, a meta-analysis could not be performed. Four studies directly comparing injection of different bulking agents found that Macroplastique and Durasphere produced equivalent improvement at 12 months to Contigen. One multicentre randomized controlled trial was retrieved that compared surgery (Burch colposuspension, sling, bladder neck suspension) to Contigen injection in 133 women with pure or mixed stress urinary incontinence. Patients who received Contigen were treated on an outpatient basis under local anesthesia, and were permitted to have up to three injections at one-month intervals before the treatment was considered a failure. Success was defined as having a dry 24-hour pad test and no additional interventions after 12 months. The success rate at 12 months after Contigen injection was significantly lower than that after surgery (53.1% versus 72.2%; p=0.01). However, the general and disease-specific quality-of-life scores were not significantly different (p=0.306) between the two groups at 12 months. Women treated by surgery were, on average, more satisfied (79.6%) than those treated by Contigen injection (67.2%), but the difference was not statistically significant (p=0.228). Finally, complications were significantly less frequent and severe with Contigen injection (36
events in 23 subjects versus 84 events in 34 subjects for surgery; p=0.03). In addition to greater postoperative pain, surgery was associated with more events of complete retention greater 48 hours after surgery (9 versus 1; p=0.001, transient difficulty voiding (24 versus 11; p=0.02), and urinary infection (4 versus 0; p=0.002). Rates of transient hematuria did not differ between the two treatment groups (8 events each). The authors argued that although therapy with Contigen produced a 19% lower success rate at 12 months than that of surgery, this result should be balanced with similar changes in quality of life and satisfaction in both groups as well as the number and severity of complications. Longer follow-up is necessary to ensure that the difference in success rate at one year remains stable with time.

While no randomized controlled trials assessing Zuidex have yet been published, several observational trials provide some evidence for efficacy and long-term safety. The first study of transurethral endoscopically administered Zuidex involved 20 patients with SUI, 6 of whom had previously received surgery for SUI or prolapse. Safety was assessed by infection rate, need for catheterization, residual urine, and dysuria. Treatment efficacy was estimated objectively by a short-term pad test with standardized physical exercise and a 48-hour pad test. Objective cure was defined as leakage less than 8g per 24 hours in the 48-hour pad test or less than 1g in the short-term pad test. Objective improvement was considered to be a reduction of incontinence by 50% in the 48-h pad test and/or in the short-term pad test. At 3-7 months follow-up, an objective cure or improvement rate of 85% was observed (45% and 40%, respectively). Four patients required catheterization due to voiding problems during the first 24 hours postoperatively. One patient reported urinary retention 14 days postoperatively. No urinary tract infections or local infections were detected. Seven patients experienced urgency and increased frequency of micturition within one month after treatment. In five of these cases, symptoms resolved with anticholinergic drugs within 3 months and in the other two patients, symptoms persisted after 6 months. In a follow-up study, only 25% of patients reported recurrence incontinence after a mean follow-up of 6.5 years and no long-term adverse effects were reported. Administration of Zuidex via the implacer device has been investigated in two European studies, both involving surgery-naïve patients in whom ISD or hypermobility was not determined. In a 36-month pilot study (n=42), significant improvements in median urine leakage (with jumping jacks or vigorous coughs) and number of incontinence episodes per 24 hours were observed at 12 months (both p<0.0001 versus baseline). Significant improvements over baseline were also noted in quality of life measures. No significant differences in median urine leakage occurred during a 24-month followup of 20 participants and no further treatment-related adverse events or complications were reported. In the second open multicentre study (n=142), a positive response to treatment was defined as a reduction in urine leakage as a result of an exercise routine of at least 50% relative to baseline. The protocol consisted of an initial injection followed by another at 8 weeks if required. A total of 61 patients (43%) underwent the second injection. The response rate was 78% and 77% of patients at 12 weeks and 12 months, respectively. After 12 months, significant reductions (all comparisons P<0.001 versus baseline) were observed in median urine leakage (93%), 24-hour pad weight test
leakage (89%) and the number of incontinence episodes per 24 hours (67%). Significant improvements were also noted in global assessment of incontinence problems and quality of life over 12 months. Treatment-related adverse events occurred in 81 (57%) of patients. Urinary retention was the most common with 29 occurrences (14 of which were classified as serious requiring hospitalization and routine catheterization) and all resolved during the study (median duration 3 days). Other treatment-related adverse effects included urinary tract infection (17 occurrences), micturition urgency (17 occurrences), dysuria (11 occurrences), injection site reaction (11 occurrences), vaginal discomfort (10 occurrences), cystitis (8 occurrences), injection site pain (6 occurrences), injection site infection (3 occurrences, all classified as serious), fever (6 occurrences), and micturition frequency (5 occurrences). In addition, an injection site pseudocyst was reported in six patients, one of which was classified as serious. Four of these were drained and all six resolved (median duration 175.5 days). The lack of significant deterioration in urinary leakage during the first 12 months after treatment in this study suggests that patients initially responding to treatment with Zuidex may continue to benefit for an extended period of time.

A recent case report indicates that there is a risk of granuloma developing locally secondary to Zuidex injection.16 Larger long-term studies are still needed to complete the safety profile of Zuidex. An ongoing randomized double-blind multicentre trial is being conducted in women with SUI comparing the safety and efficacy of Zuidex to Contigen.17,18 Eighteen centers in the US and Canada will treat about 260 patients and each patient will be followed up for 12 months following treatment. Participants must be females over the age of 18 who have a history of SUI (for at least 12 months) and have failed prior non-invasive treatment (such as pelvic floor exercises and biofeedback), but have not received prior treatment with a bulking agent for SUI.

**Economic considerations:**
Health economic data for periurethral injection therapy is very limited. From the patient’s perspective, pads are likely to be the major source of expenditure, so any treatment that reduces pad usage should provide substantial cost savings. From the perspective of the healthcare system, costs of materials used (e.g. slings or injectable agents), equipment required, type and duration of procedure, treatment of adverse effects, postoperative care, and the need for re-intervention in the case of insufficient efficacy are all important considerations. The objective of one economic analysis19 was to investigate utility (patient preferences for given health states) with Zuidex therapy and to compare cost of Zuidex treatment with tension-free vaginal tape (TVT). Utility was measured using EuroQol (EQ-5D), a generic instrument. For the cost of Zuidex treatment, data was collected prospectively from participants in a 12 month open-label single-arm efficacy study13 (n=82). Retrospective analysis of a comparable group of patients (n=77) with 3-6 months follow-up was used to obtain equivalent costs for TVT. Costs were analysed for both Sweden and France. Results indicated that injecting Zuidex via the implacer had lower overall costs than TVT (22,435 versus 28,954-32,019 Swedish krona per patient) while offering at least similar utility gain (0.03-0.09 vs. 0.03 for TVT). Furthermore, Zuidex decreased pad usage by 58% over a 12 month period, translating into substantial savings for the patient over time.19 The authors concluded that Zuidex
could be considered at least as cost-effective as TVT, pending the availability of long-term effectiveness data. However, these results are limited by the fact that the study did not use a more robust method to compare the two treatment options.

Another economic study evaluated the cost-effectiveness of surgery versus Contigen injection to treat female SUI after the failure of initial surgical treatment. The analysis was conducted from the health care system perspectives of Ontario and Quebec. A decision-tree analysis was constructed to compare Contigen injection with three types of surgical procedures (retropubic suspension, transvaginal suspension, or sling). The incremental cost-effectiveness ratios to cure an additional patient with surgery ranged from C$1824-6814 in Ontario and C$1388-3008 in Quebec. The ratios were sensitive to changes in mean number of injections and a reduction in the length of hospital stay for surgery. The results suggested that while overall cost was lowest with Contigen, the lower likelihood of cure with this treatment made surgery more cost-effective as first-line therapy. The authors concluded that therapy with Contigen may be cost-effective as a follow-up treatment to surgical failure assuming the number of injections were minimized and post-surgery hospital stays were relatively lengthy.

Conclusions and implications for decision or policy making:
In summary, the available evidence for Zuidex evaluation is very limited. Only low quality evidence from small short-term uncontrolled observational studies currently exists. Results indicate that Zuidex may be a promising alternative to surgery for SUI in those failing non-invasive therapies. Its efficacy in those who have not achieved symptom control with surgery is not yet clear. Similar to Contigen, some patients require multiple injections. While there is some long-term data, larger trials are needed to confirm the safety and efficacy of Zuidex.

One potential advantage of Zuidex over Contigen includes the lack of a requirement for prior allergy skin testing. Furthermore, Zuidex can be administered without the need for endoscopic guidance. This reduces the level of equipment and facilities required for treatment, potentially increasing cost-effectiveness as well as convenience for the patient. Given current cost constraints, well designed randomized controlled trials comparing Zuidex with other treatment alternatives are required to fully assess clinical and economic benefit. Ultimately, cost-effectiveness should be confirmed with longer-term studies that account for treatment of complications and patients who eventually go on to receive more invasive surgery. Until higher quality evidence is available, the decision of when to use one injection bulking agent over another as an alternative to surgery must be based on costs specific to the particular institution and on clinical experience.

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