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ORIGINAL ARTICLE

The safety and efficacy of ethylene vinyl alcohol copolymer as an intra-urethral bulking agent in women with intrinsic urethral deficiency

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Abstract The purpose of this post-marketing case-series is to report the short-term safety and effectiveness of ethylene vinyl alcohol (EVA) copolymer (Tegress™; C.R. Bard, Covington, GA, USA) in the treatment of intrinsic sphincter deficiency (ISD). The charts of all female patients who received ethylene vinyl alcohol (EVA) copolymer between 2005 and 2006 were reviewed for demographics, physical exam, urodynamic findings, outcomes and complications. Nineteen of twenty women who received EVA during this period completed follow-up. After an average of 1.4 injections, ~58% of the patients had a complication related to the procedure with 37% experiencing urethral erosion. Of the patients, 10.5% reported at least a 50% subjective improvement in their symptoms. Intra-urethral bulking for the treatment of SID is meant to be minimally invasive and safe with minimal reports of complications. This series of 19 patients show significant percentage of patients experiencing serious complications with Tegress™. Additionally, Tegress™ may be less efficacious than reported in the FDA trials, especially those with prior injections. A long-term prospective study needs to be performed in women with ISD before treatment can be recommended for general use by all gynecologists and urologists.

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Introduction

Intra-urethral bulking agents have been used for nearly 70 years in the treatment of stress urinary incontinence (SUI). As defined by the International Continence Society, SUI is the complaint of involuntary leakage of urine upon effort or exertion, such as coughing or sneezing [1]. More specifically, bulking agents have been primarily used for patients diagnosed with intrinsic sphincter deficiency (ISD). ISD, also known as type III incontinence implies a low-pressure urethra with "normal" support [2], although various leak point pressure and urethral closure pressure cutoffs were also used as defining characteristics. In addition, patients with SUI who do not meet the criteria for ISD and are poor candidates for surgery or those who desire to avoid a surgical procedure are also candidates for this therapy. The ideal intra-urethral bulking agent is one that is non-immunogenic, hypoallergenic, biocompatible, heals with minimal fibrosis and retains its bulking effect over a long period of time without migration [3].

Intra-urethral bulking agents were initially introduced in 1938 with sodium morrhuate being injected into the anterior vaginal wall [4]. Since that time, numerous other injectable bulking agents were introduced. In the 1970s and 1980s, polytetrafluoroethylene was commonly used. Unfortunately, this agent had a poor safety profile secondary to distant migration leading to granuloma formation in organs such as the spleen, brain, lungs and liver [5]. This product was subsequently replaced by bovine cross-linked collagen

(Contigen™). Its advantages included ease of injection, lack of migration risk and biocompatibility. Although Gorton et al. reported a 70% short-term success rate; over time they found poor long-term outcomes, bringing to light collagen's lack of durability [6]. In addition, skin testing must be performed at least 1 month before the initial collagen injection because of hypersensitivity risks associated with the product. Improving upon collagen, carbon-coated zirconium beads (Durasphere™) were later created in an attempt to find a product meeting the criteria described above. Unlike collagen, carbon-coated zirconium beads (CCZB) are permanent and hypoallergenic. In a study by Lightner et al., they were found to be equally effective as bovine cross-linked collagen in the treatment of ISD with an 80% improvement by at least one continence grade at 1 year. Relative to collagen, CCZB were associated with an increased short-term risk of urinary retention and urgency [7]. An extended follow-up report by Chrouser et al. found that CCZB did not provide long-lasting improvement in continence [8]. Another difficulty with this product lies in the difficulty of injection of the material due to the size of the beads.

Research has continued to explore new agents for injectable therapy. While striving to develop a more optimal injectable agent, ethylene vinyl alcohol copolymer (Tegress™ or formerly Uryx®), a product previously utilized as an implant in other medical situations, has now been recently approved by the FDA and marketed as an intra-urethral bulking agent. The product is dispensed in a dimethyl sulfoxide (DMSO) carrier; a clear and odorless solution that once injected diffuses into the tissue. The ethylene vinyl alcohol copolymer (EVA) then precipitates into a material that becomes a soft, spongy, hydrophilic implant that in theory reinforces the integrity of the urethral mucosal seal [9]. Tissue remodeling occurs over time as fiber ingrowth incorporates the implant into the native host tissue. In the trials for FDA approval, EVA was reported as achieving complete dryness or greater than 50% improvement compared to baseline at 12 months after an average of 2.1 treatments (http://www.bardurological.com/resources/product/procApps/Tegress_procedural_apps.pdf Accessed April 2006). At this time, there are no published studies from the data for FDA approval. The purpose of this post-marketing case series is to report the authors' experience with the safety and efficacy of EVA used as an intra-urethral bulking agent in the treatment of female ISD by a surgeon with considerable experience with bulking agents and their administration (RAA).

Materials and methods

A retrospective review of all adult female patients who underwent an intra-urethral bulking with EVA from 2005 to 2006 for the treatment of ISD in the senior author's practice was performed. Patients who received bulking agents other than EVA were excluded in this case series. All patients underwent a thorough medical history, physical examination and urodynamic study. After determining the diagnosis of SUI or mixed incontinence, appropriate patients were offered intra-urethral bulking agents based upon a low leak point pressure and/or fixed urethra. At post-injection follow-up visits, patients were asked to state their improvement scores on a scale from 0% to 100% with 0% being no notable change since the first EVA injections and 100% being completely dry. This method was used to help the patient and physician determine if further injection sessions were needed. Charts were reviewed for demographic, urodynamic data, subjective improvement and complications.

For 20 patients, the injection of EVA was performed under local anesthesia in the outpatient urodynamic suite. All injections were performed transurethrally after the administration of 2% intra-urethral lidocaine gel and periurethral block of 1% lidocaine (8 ml). Before injection, EVA in a DMSO carrier solution was aspirated into a 3 cc syringe. A rigid 0° or 30° cystoscope was then passed through the urethra and into the bladder where the 3-French stainless steel shaft with a 25-gauge non-coring needle tip was deployed. The needle was then inserted into the mid-urethra and the material was injected into the submucosa of the proximal urethra, generally at 3 and 9 o'clock. For patients with a poorly coapted urethra, 1–1.5 ml per side of EVA was injected. If the patient already had a fair degree of urethral coaptation or erosion of material on one side was present, the material was injected into a single side. Per protocol, each injection took place over 1 min. An additional minute was needed for the chemical reaction and solidification of the material before needle removal. Patients waited in the suite until they were able to void. If they were unable to void, catheterization with a 12-French straight catheter was performed. If the patient did not achieve continence, a 90 day waiting period was allowed before the next injection. Patients were given 48 hours of prophylactic oral antibiotics post-procedure.

Results

Twenty female patients underwent intra-urethral bulking with EVA during the time period of the review. Complete follow-up information was available on 19 patients. The mean age of the patients was 66.3 years (41–86 years). These women had undergone a mean of 1.0 prior anti-incontinence surgical procedures and a mean of 2 prior injections with other materials such as CCZB (Durasphere™), collagen (Contigen™) or calcium hydroxyl

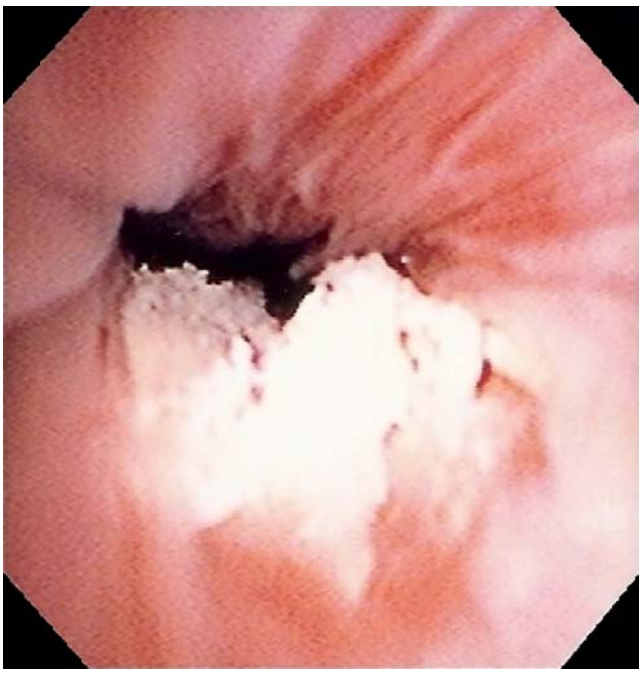

Fig. 1 Cystoscopic view of urethral erosion

coapatite (Bioform™) with three patients never having had intra-urethral bulking. Of the 20 patients, 18 did not demonstrate urethral hypermobility (Q-tip angle of less than 30° while straining) on physical exam. Of the two patients who did have urethral hypermobility, both had prior mid-urethral slings. On urodynamic testing, the mean leak point pressure was 51.9 cm H_2O. All patients demonstrated SUI, while three patients had mixed incontinence with abnormal detrusor contractions being noted only after a valsalva maneuver. The patients received a total of 27 injections. The mean number of injections was 1.4 and the mean volume injected per session was 1.7 cc. The mean follow-up time was 4.5 months with 10.5% of the patients reporting at least a 50% subjective improvement in their symptoms. Of the 20 patients, 13 (68%) reported no improvement in their urinary symptoms.

Complications related to the procedures were noted in 58% (11) of the 19 patients with follow-up. The most common complication was erosion of the material into the urethra at 37% (Fig. 1). Three of seven patients were asymptomatic and the material was incidentally found at the time of cystoscopy for repeat injection. This finding precluded injection in that area of the urethra on the subsequent sessions. Four patients were symptomatic with extreme dysuria requiring multiple follow-up visits in the office. Two of the four symptomatic patients passed the material spontaneously with subsequent resolution of their symptoms and a concomitant increase in their stress incontinence symptoms. One patient did not pass any material, but had re-epithelialization of the urethral mucosa over several months resulting in resolution of the symptoms. An additional patient required cystoscopy to remove the eroded material to alleviate her symptoms. Of the 19 patients, 10 had urinalysis performed after the procedure. Four (40%) patients had microscopic hematuria noted up to 3 months after the procedure (two of these patients also experienced erosions). One patient with both erosion and microscopic hematuria was diagnosed with a urinary tract infection confirmed by urine culture. One other complication was technically related, with the needle clogging, resulting in the procedure being prematurely terminated. Additional complications included urinary retention, which was noted in one patient and required 5 days of self-catheterization, while another patient reported severe urgency symptoms that required anticholinergic therapy (this patient did not have evidence of implant erosion post-procedure or any abnormal detrusor contractions pre-procedure).

Discussion

All of the previous materials used for intra-urethral bulking agents have failed to meet the criteria for the "ideal" agent. EVA (Tegress™) was touted to meet many of these criteria by being an agent that is permanent, non-immunogenic and biocompatible. In addition, the liquid formula via a transurethral approach simplifies the injection technique. Theoretically, this should lead to a long-lasting effect with minimal complications.

Of utmost importance in this case series is the issue of the safety of EVA as an intra-urethral bulking agent. Our experience with a complication rate of 58% does not differ greatly with the early clinical trials where 72% of 174 patients receiving a total of 374 injections received at least one adverse treatment effect. In the clinical trials, the most common complications were urinary tract infection, delayed voiding, dysuria, exposed material, urinary urgency and frequency, hematuria and genitourinary tenderness. It is interesting to note that in our case series the erosion rate is much higher at 36.8% compared to 16% [10]. This erosion rate is of concern considering the amount of discomfort experienced in four of the seven patients and the associated medical attention these patients required. In addition, these patients also reported loss of whatever benefit was obtained after passage of the material. One could postulate that our patients had a higher erosion rate due to the suboptimal injection technique, however all injections were performed according to the manufacturers' recommendations. Further, the injections were all performed by a physician (RAA) experienced in performing intra-urethral bulking procedures and endoscopic procedures. Another possible explanation for the high erosion rate is that a significant portion of our patients had received prior bulking agents where these

patients would have been excluded in the clinical trials. It is plausible that the urethra's mucosal blood supply was compromised in these patients, especially when combined with prior surgery. However, it is important to include these patients in reports because injectable therapy is an appropriate treatment for ISD regardless of having undergone prior injections, especially when prior injection therapy has failed due to the material's properties. Our hypothesis for the higher erosion rate is that it is secondary to the chemical reaction that occurs during the injection as the DMSO is washed away. It is possible that this may disturb blood flow to the urethral mucosa, thus predisposing it to erosion.

Complications with this material also exist in other medical arenas where it was approved for use. Marketed as Enteryx®, EVA was previously used to treat gastroesophageal reflux by injecting it into the gastroesophageal junction. After two deaths and numerous complications, especially concerning the migration and erosion of the material through the vessel walls, Enteryx® was removed from the market. Most of the complications arose from unrecognized transmural injections. One death was from suspected erosion into the wall of the aorta resulting in an aortic–enteric fistula [11].

Concerning the efficacy in our subset of patients, only 10.5% of patients reported at least a 50% subjective improvement in their stress urinary incontinence symptoms. Of the 19 patients, 13 were unable to report any subjective improvement after 4 weeks after the last injection. In the trials for FDA approval based on the intent to treat, 18% were dry and 49% were dry or improved by one Stamey grade, 50% had a 50% improvement in pad weight and 22% reported a greater than 50% improvement on the IQOL validated survey [10]. Our lower success rates may be due to several factors. First, the method used to assess patients subjectively was not validated as a reliable and reproducible method. In addition, the average of 1.4 injections given to the patients during this time period may not have been sufficient to attain the results in the clinical trials. The high rate of erosion and other complications limited our ability to re-inject patients who were still complaining of incontinence because of both patient dissatisfaction and concerns with re-injecting areas already eroded. In addition, when we did re-inject patients we were often limited to injecting only part of the urethra because of unilateral exposures. Another possible factor resulting in our poor success is that our patient population had already received an average of 2.1 prior injections of other materials and an average of 1 prior surgical procedure for urinary incontinence. In the clinical trials, patients were excluded if they had received a prior injectable agent. Our patient population may represent one with significantly worse disease. Another potential factor limiting the effectiveness of this product is the inability to adequately judge coaptation during the injection. Instead one must rely entirely on product expansion over a period of time to appropriately coapt the urethral mucosa. Further, material lost through erosion may contribute to the loss of continence.

This case series brings forth many questions regarding the safety and effectiveness of EVA used as an intra-urethral bulking agent. To date, there are no other reports available outside of industry sponsored clinical trials. Of concern is the erosion rate that may be much greater than previously estimated. An inherent weakness in our case series exists in that our series did not have objective data or a validated survey to quantify subjective improvement or quality of life. Studies showed the inaccuracies of patient's subjective data vs more objective data such as urodynamic testing [12]. Additional weaknesses in this study include recall bias, which is inherent in any retrospective study. However, it could be postulated that a patient who notes no subjective improvement on a scale from 0% to 100% would be unlikely to show significant improvement on a subjective, validated questionnaire.

Intra-urethral bulking for the treatment of ISD is meant to be minimally invasive and safe with minimal reports of complications. This case series of 19 patients shows a significant percentage of patients experiencing serious complications, such as erosion with Tegress™. These erosions were responsible for severe dysuria causing distress in several patients. In addition, Tegress™ may be less efficacious than reported in the FDA trials, especially in those with prior injections. Larger, long-term, prospective studies with serial cystoscopy, objective testing and validated questionnaires need to be performed in women with ISD before this treatment can be recommended for general use by all gynecologists and urologists.

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