Comparison of Autologous, Non-autologous, and Synthetic Periurethral Bulking Agents

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Abstract

Periurethral bulking agents have been in development since 1938. There are currently four FDA approved agents, along with eight materials currently under investigation. A bulking agent must be injectable, biocompatible, non-migratory, and have the desired biodegradation properties. No bulking agent has yet shown the ability to meet all four requirements sufficiently. Many mechanical and biological factors play an important role in the overall function of the agent. For example, viscosity affects injectability, and surface properties affect biocompatibility. Ethyl vinyl alcohol copolymers seem to be the most effective of the currently approved treatments due to the injection method and overall durability. There are many materials currently under investigation seeking to improve upon the properties of the current periurethral bulking agents.

1. Introduction

Urinary incontinence is a prevalent problem, moderately or severely affecting as many as 17% of women and 11% of males [1]. However, many others have occasional incontinent episodes, which tend to increase with age (Fig. 1) [1]. Incontinence is divided into subcategories, with the most common being stress urinary incontinence (SUI). SUI occurs when abdominal pressure increases, due to laughing, coughing, sneezing, etc., leading to urinary leakage. The two broad causes of SUI are urethral hypermobility and intrinsic sphincter dysfunction (ISD). Urethral hypermobility is an anatomic defect that is effectively treated with a pubovaginal sling that corrects the anatomy of the urethra [2]. ISD is caused by weakening of the musculature surrounding the urethra [2]. In normal urethral function, the pressure in the urethra generated by the muscles exceeds the pressure in the bladder. When one decides to urinate, the muscles relax allowing the urine to flow. However, the musculature around the urethra is not strong enough in a patient with ISD to oppose the bladder pressure when there is increased abdominal pressure, leading to leakage [3]. Risk factors for ISD include child birth and menopause for women, prostate removal for men, and advanced age for both men and women [2]. There are a variety of possible treatments for ISD, including various pubovaginal slings and injectable periurethral bulking agents. Use of a pubovaginal sling has been shown to be effective, but implantation of a sling requires major surgery that a high majority of those affected by the disease, elderly men and women, may not be able to endure [4]. Therefore, periurethral bulking agents, which are minimally invasive and only require local anesthesia, have been pushed to the forefront of ISD research.

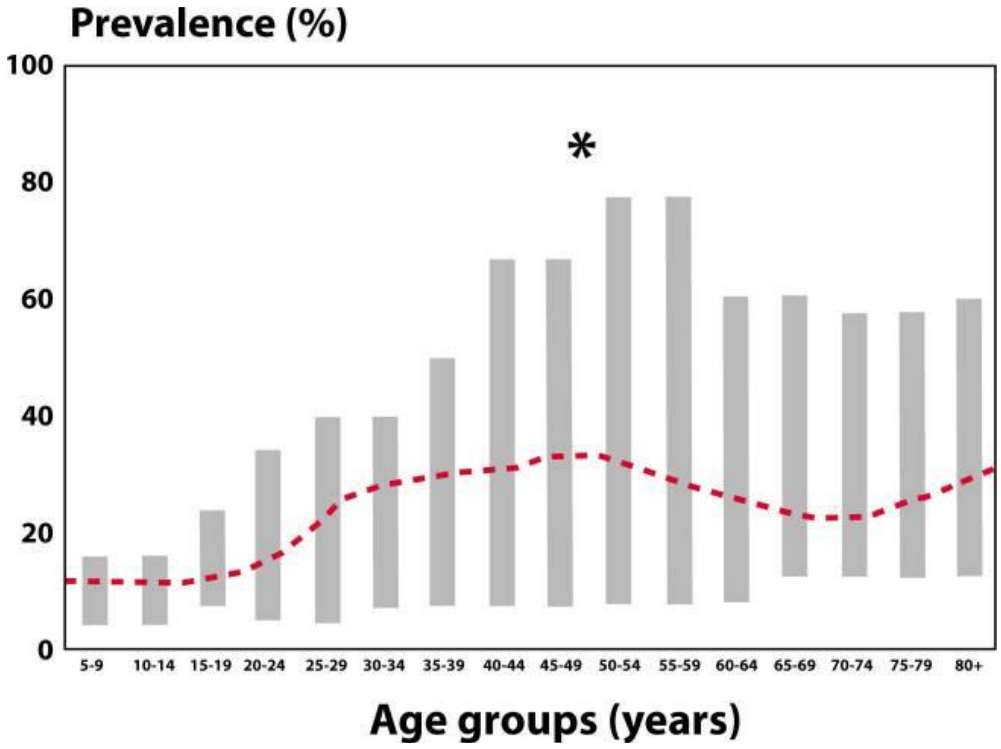

Figure 1. Prevalence (%) of incontinence in general population of females reported in 13 different studies. Young adult, 20% to 30%; Middle age, 30% to 40%; Elderly, 30% to 50%. Peak prevalence represented by (*), and average is represented by dashed line [1].

Periurethral bulking agents are materials that are injected around the urethra to compress it and increase its resistive pressure relative to the bladder pressure. The first reported use of periurethral bulking agents was by Murless in 1938 with the use of sodium morrhuate solution, which had a 60% success rate [5]. Since then, many different materials have been and are presently being developed. As of now, four bulking agents have been approved by the FDA: bovine gluteraldehyde crosslinked (GAX) collagen, pyrolitic carbon-coated zirconium beads (PCZBs), calcium hydroxylapatite, and ethylene vinyl alcohol copolymers (EVACs) [4,6,7]. Approval by the FDA of the use of microballoons is pending. PTFE (Teflon), hyaluronic acid and dextranomer microspheres, and silicone microimplants are currently being tested in Europe [4]. Finally, the use of bioglass and also tissue engineered constructs with autologous cell sources have been investigated [4]. Clearly the field of periurethral implants is a very diverse and dynamic one. These various bulking agents can be classified into one of three groups: autologous (cell source is from the patient), non-autologous (cell source is not from the patient), and synthetic (material is not biologically derived). These three types of bulking agents will be further examined and compared with regards to their structure and functions.

2. Performance Requirements of Periurethral Bulking Agents

Before discussing the individual bulking agents, it is important to understand the general performance requirements of urethral bulking agents. First and foremost, the material must be injectable. Typically, after local anesthesia is applied, a needle is inserted and run along the

urethra, and then the material is injected in various positions around the urethra (commonly at the 3, 6, and 9 o'clock, or 4 and 8 o'clock positions) (Fig. 2) [8]. Once the material is deemed injectable, it must also be considered biocompatible. Once in the body, it cannot cause excessive infection, allergic reaction, or other serious immune response. There are many materials that match the first two requirements, but urethral bulking agents must also be non-migrating and non-degradable [2]. The agent is placed in a way to compress the urethra and prevent incontinence. However, more injections will be needed if the material is degraded over time or if it migrates to other parts of the body. Migrating particles could also cause more serious health problems depending on the material and where it ends up in the body. One last requirement is for the material to be low cost, as a perfect implant that has an extremely high cost may still not gain widespread use. All of the aforementioned materials currently in use or under investigation meet some, but not all, of these requirements.

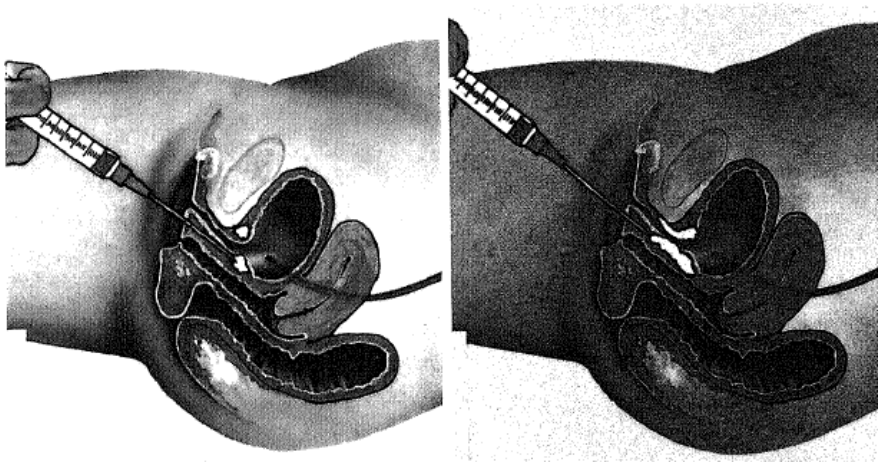

Figure 2. Injection of a bulking agent into a female. The Bulking agent is injected as the needle is pulled out, leaving a line of bulking agent along the outside of the urethra [8].

3. Injectability

The primary requirement for a periurethral bulking agent is that it is injectable. The main material property that controls this is viscosity. Many of the agents studied are viscous gels, such as the collagen, fat, and various hydrogels. However, the agents with microparticles, especially PCZBs and microballoons were initially difficult to inject. PCZBs were initially relatively large microparticles (approximately 300 μm) which were very beneficial when it came to preventing migration throughout the body, but made injection difficult [9]. The lack of injectability led to surgical mistakes in placement of the spheres. In order to combat this problem, smaller spheres were produced; however, this led to increased migration [6].

Microballoons are also relatively large, but in order to make injection easier, the balloons are inserted while deflated. After implantation, the balloons are inflated to their full size, improving injectability [10]. Another way that various materials become more injectable is by using a carrier gel or liquid. For example, silicone microimplants are injected with a mixture of 40% silicone with 60% povidone hydrogel [11]. The povidone provides lubrication for the microimplants in order to make them more injectable.

An interesting technique for improving injectability is found in EVACs. EVACs are soluble in DMSO at room temperature; however, when placed in physiologic temperatures and solutions, the DMSO diffuses from the copolymer, allowing the EVACs to precipitate into a spongy bulking agent (Fig. 3) [10]. This allows for easy injectability, and also a robust solid bulking agent. Overall, injectability is important for surgical precision, but often requires sacrifices in other performance requirements are sometimes necessary.

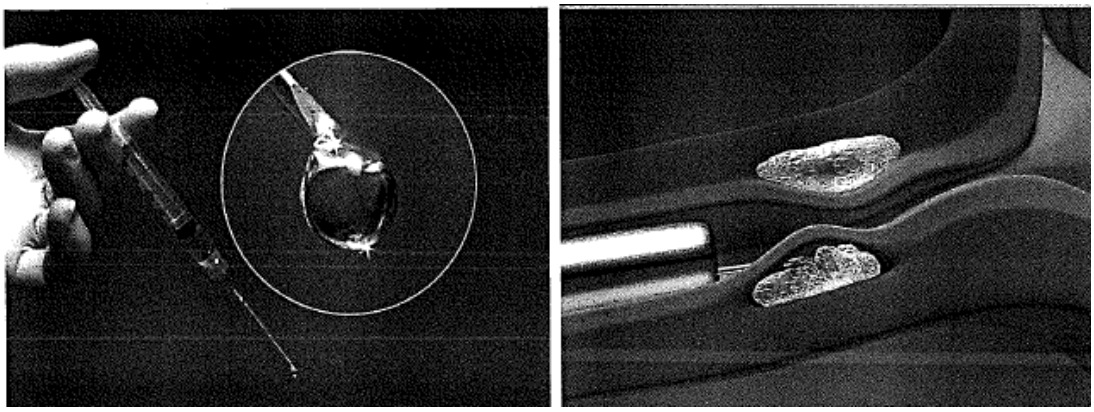

Figure 3. Left: Clear EVAC liquid at room temperature, prior to injection, Right: Gelatinous compound after transurethral injection [7].

4. Biocompatibility

In order to ensure that the patient's body will not reject or have an allergic reaction to the implanted material, it is essential to verify that the material is biocompatible. Most of the bulking agents have been shown to be biocompatible; however, some of these materials have elicited allergic reactions and inflammation. Biocompatibility, with regards to periurethral bulking agents, is typically measured by evaluating patient health over time. After injection, the patients are observed for any side effects associated with the treatment; if there are no serious side effects, the material is considered biocompatible. An *in vitro* test in which cells are seeded onto the agents and cellular proliferation and adhesion are measured would be a useful test for assessing biocompatibility. Utilization of an animal model for *in vivo* testing would also be helpful. Nonetheless, neither *in vitro* nor *in vivo* testing in animals has been performed to date. GAX-collagen is a non-autologous agent, and is typically acellularized and chemically treated in order to prevent rejection. However, there have still been rare, but serious cases, of a delayed hypersensitivity reaction occurring in approximately 4% of female patients [6,10]. The synthetic material PTFE has never received FDA approval as a bulking agent, mostly due to biocompatibility concerns with the material [12]. PTFE has been shown to elicit an immune response, and through phagocytosis, it has migrated to other parts of the body and formed foreign body granulomas [4]. These granulomas have been found in the lungs, brain, kidney, lymph nodes, and spleen of laboratory animals [12]. In rare cases, the granulomas have formed around the urethra and have closed it completely [13]. The fact that non-autologous sources still illicit an allergic response, even after chemical treatment, and that synthetic materials can illicit an immunogenic response has led many researchers to focus on the use of autologous sources.

The two most prevalent autologous sources are autologous fat and cartilage. Since the cells in the tissue come from the patient, the patient's body will recognize the cells and have no response to them. Fat is usually removed and then placed directly around the urethra with little post-processing [14]. Cartilage is harvested (typically from the patient's ear lobe), expanded, seeded in a degradable hydrogel (commonly alginate), and then implanted. The hydrogel dissolves over time and new vasculature and matrix is made in order to add bulk around the urethra [15]. Considering just biocompatibility, the autologous cell sources are clearly the most effective.

5. Migration

One of the most challenging issues facing the use of periurethral bulking agents is migration of the bulking agent. The particles must be small enough to be easily injectable with a reasonably sized needle (Fig. 4), but yet large enough to stay near the urethra [4]. PTFE particles (between 4 and 100 μm) were injected into dogs and monkeys to investigate migration away from injection site [16]. The largest PTFE particle found to have migrated was 80 μm; therefore, 80 μm is the accepted threshold for particle migration away from the urethra [16]. Larger PTFE particles could have migrated without the researchers finding them, however, which means that larger particles may be able to migrate. Heterogeneous particle sizes are one factor that affects migration. For instance, PTFE ranges between 50 and 300 μm, therefore the majority of particles do not migrate. However, enough particles fall under the 80 μm threshold and migrate, which can cause serious health risks elsewhere in the body.

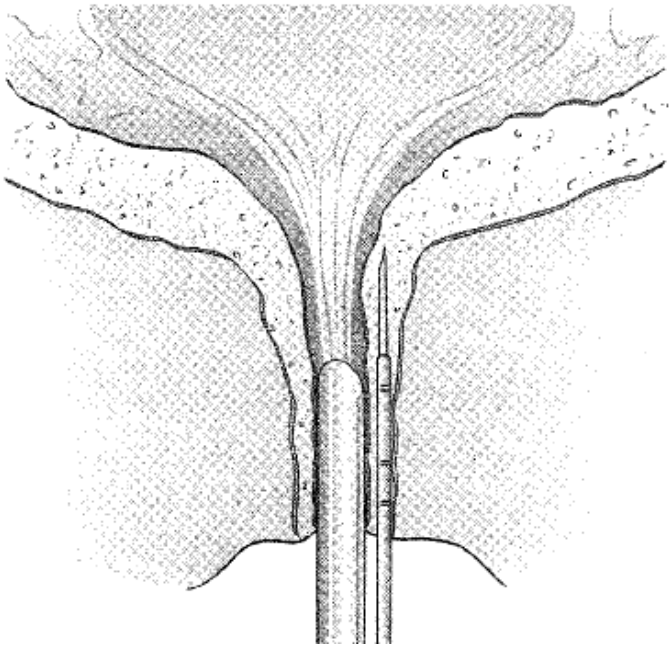

Figure 4. Technique for periurethral injection. 20-gauge needle and cytoscope are shown. Cytoscope is placed inside the urethra, while the needle is placed in the musculature around the urethra. The bulbous shape at the top of the figure is the bladder [4].

PCZBs were originally 200-550 μm, but due to injectability issues their size has been decreased to 95-200 μm [6]. PCZBs with the decreased particle size have been reported to migrate to lymph nodes [17]. The fact that the PCZBs minimum size is 95 μm, but they still migrate, calls into question the widely used threshold of 80 μm. Nonetheless, one of the most prominent techniques used to prevent migration is to increase particle size.

Two other, more elegant, approaches are also utilized to prevent migration. First, biological materials, such as collagen, fat, and cartilage, are usually implanted with the knowledge that the body will integrate and replace the implant. Once there is fibroblast ingrowth and vascularization of the implant, the tissue bolus that is formed prevents migration and helps to further add bulk around the urethra [10]. However, there has been one reported case of a fat droplet migrating and forming an embolism causing the death of a patient [18]. Other non-biologic materials use similar principles. For example, hyaluronic acid is biodegradable and dissolves within 2 weeks [19]. However, hyaluronic acid recruits fibroblasts and triggers vascularization before dissolving, leaving behind a spongy extracellular matrix which achieves the bulking. Similarly, calcium hydroxylapatite, the mineral found in bone and teeth, has been shown to adhere to collagen fibers [10]. Bioglass is a composed of calcium oxide, calcium silicone, and sodium oxide, and has been shown to exhibit good cell adhesion, preventing migration after injection [20].

Overall, migration of particles can lead to serious health issues, and even death, and is therefore of critical importance in the design of improved periurethral bulking agents. The biologic and biologically active agents have the advantage over others due to the ingrowth of tissue to prevent migration of the agent.

6. Biodegradation

Biodegradation can be both a benefit and a hindrance depending on the material. For example, the main concern with GAX-collagen is its degradation over time. As the GAX-collagen degrades, the periurethral bulk is lost as well, and this is followed by the return of urinary incontinence. This leads to more injections which are painful and, overtime, become costly [10]. The autologous chondrocytes in a hydrogel, however, require the hydrogel to degrade over time in order to allow greater tissue ingrowth. As the hydrogel degrades, more tissue can grow, creating a more long term treatment [15]. All of the synthetic materials such as the PTFE and PCZBs have been shown to maintain their volume over time, which leads them to be more durable and permanent solutions [4]. Biodegradation is a very important factor with regard to patient cost and satisfaction due to the possibility of repeat injections.

7. Current Limitations

There are two major difficulties in assessing the efficacy of a periurethral bulking agent relative to other agents. The first difficulty facing the research of bulking agents is determining a set of tests that can be used to assess whether or not the patient is "cured." There are several diagnostic questionnaires given in order to assess the level to which the incontinence affects the patient's daily life and their quality of life. The Valsalva leak point pressure is also commonly used to diagnose incontinence. This pressure is defined as the lowest total bladder pressure at which leakage occurs during progressive increases in abdominal pressure by the Valsalva maneuver [3]. The test is simple and a good tool, but due to differences in the administration of

the test there is a lack of standardization. Another common test used is pad weight. Usually, a person with a full bladder is asked to perform a variety of exercises that would induce abdominal pressure and an incontinence episode while wearing a pad. The pad is weighed before and after to determine the amount of leakage [10]. This test is usually performed before treatment and at various time points after treatment to assess improvement. There are other techniques used, such as MRI for anatomic defects, but there is no standardized way to assess the efficacy of a treatment. The lack of a standardized measurement makes it extremely difficult to compare results from different studies.

There is also little research being performed on the mechanical properties of periurethral bulking agents since most of the focus has been clinically oriented. Most clinical research has focused on showing that one agent is more effective than another based on "cure" rates. While this is important, there is very little focus on why the material is more effective. A stronger focus on the structure and properties of the bulking agents could lead to large advancements in clinical effectiveness. Understanding the structure-property relationships of the materials can lead to a greater understanding of why the materials are injectable, biocompatible, migratory, and degradable. For example, viscosity measurements of the materials could lead to new insights on injectability. A study on surface properties of the bulking agents and how this affects protein adsorption and overall biocompatibility would also be invaluable. In vitro testing of the materials for tissue ingrowth would lead to new information on migration and biocompatibility. Understanding this information could lead to insights on what properties are and are not desirable. These insights could lead to the design of new materials that continue to approach the ideal periurethral bulking agent.

8. Discussion

An ideal periurethral bulking agent has yet to be developed. GAX-collagen is the most widely used, but major issues with rapid biodegradation and minor issues with allergic reactions remain unresolved [10]. Autologous fat is readily available, but degradation and migration have led to the death of one subject [18]. PTFE, PCZBs, and silicone microimplants tend to migrate and form granulomas which can lead to serious medical complications [10]. Calcium hydroxylapatite is also biodegradable, leading to repeat injections [10]. Microballoons have a complicated injection method, and have been shown to lose volume over time [10]. EVACs use a unique material behavior to make a material highly injectable and also durable by having the agent precipitate after injection [7]. Bioglass, autologous cartilage, and hyaluronic acid and dextranomer microspheres have not been subjected to sufficient human trials to make conclusions about their overall performance [4].

Overall, there is a necessary balance between the performance requirements. The agents need to be large enough to prevent migration, but small enough to be easily injected. The agents need to be bioactive to encourage cell ingrowth and prevent migration, but durable and non-resorptive enough to not require multiple injections. For now, EVACs seem to be the most viable option since the only drawback is that the injection procedure is somewhat complicated due to precipitation of the polymer in about 60 seconds [7].

Newer technologies such as bioglass, hyaluronic acid and dextranomer microspheres, and autologous cartilage may hold promise, but are still in early investigation. Bioglass has been effective at curing incontinence in limited studies, and its cell adhesion properties are crucial in preventing its migration. However, bioglass requires a very large needle for injection [4]. As

the necessary needle size increases, the possibility of the material extruding back through the insertion point also increases [4]. Hyaluronic acid and dextranomer microspheres have exhibited retention in the urethral region and have a high cure rate, but more human testing is necessary [4]. Autologous chondrocytes seeded in a hydrogel have the benefit of being biocompatible, easily injectable, and able to encourage tissue ingrowth which leads to a durable and non-migratory implant [15]. These three techniques have the potential to improve current bulking agents, but more long term research is necessary to ensure their safety and efficacy.

One of the most important developments needed in the field is a way to measure the clinical success of these implants. The definition of a patient being "cured," and the parameters of each study varies greatly and makes it nearly impossible to compare the results. For example, pad weight, questionnaires, and the Valsalva leak point pressure are all used as diagnostic tools to determine success and cure rate, but these all have highly subjective results. Also, the patient eligibility criteria have slight differences between studies as well.

Overall, periurethral bulking agents hold a lot of promise as a minimally invasive treatment for a highly prevalent issue. Although the ideal bulking agent is yet to be discovered, there are many effective techniques currently available and many more currently under investigation.

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