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Original Article

The Safety of Reusing Injectable Collagen: A Multicenter Microbiological Study

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Abstract: We have previously reported pilot data regarding the safety of saving partially used syringes of a glutaraldehyde cross-linked collagen for use in subsequent treatment sessions with the same individual. That single institution study involved 56 partially used syringes cultured for aerobic bacteria. Only one weakly positive culture was detected among these 56 samples, which prompted us to carry out this expanded study involving multiple centers and different injection techniques. Samples were collected from four centers. Following periurethral injection in an office setting, 166 partially used syringes of glutaraldehyde cross-linked collagen were refrigerated for between 1 and 104 weeks (average 58). Material from all 166 syringes was then cultured qualitatively and quantitatively for both aerobic and anaerobic organisms. Collagen from one syringe grew >100 000 colonies of *Escherichia coli*. All other cultures were negative. In the pilot study, one culture of 56 syringes was weakly positive for coagulase-negative staphylococcus. When the results from both studies were considered together, only two of 222 partially used syringes (0.9%) were contaminated. The background risk of local infection associated with periurethral collagen injection is approximately 0.29%. Using the statistical equation 'number needed to harm', we found that a clinician would have to reuse 111 syringes at a saving of $34,965 before he or she would cause a single local injection by so doing. Therefore, we feel that it may be cose-effective and safe to reinject material from a partially used syringe of glutaraldehyde cross-linked collagen during a subsequent treatment session on an individual.

Keywords: Collagen; Equipment reuse; Syringes; Urethra; Urinary incontinence

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Introduction

Injectable bovine collagen is widely used as a periurethral bulking agent to treat genuine stress incontinence due to intrinsic sphincter deficiency. It is available commercially in 2.5 ml syringes costing approximately $315 each. In order to achieve cure or a significant improvement of incontinence, several injection sessions are usually required. In a restrospective study of 187 women, Herschorn et al. [1] found that a mean of 2.5 treatment sessions were needed to achieve cure or significant improvement of stress incontinence in females. In that study, the mean amount of collagen injected per session was 3.8 ml, or about 1.5 syringes. Other large studies have reported similar findings [2,3]. Patients' initial injection sessions typically require the use of more collagen than is required during subsequent sessions. Because of the need for multiple injection sessions requiring less and less collagen, clinicians frequently find themselves with a significant amount of unused collagen after adequate coaptation of the urethral lumen has been achieved. At that point the physician has

two choices – either to discard the leftover material or to inject it more laterally in the periurethral area. If these partially used syringes could be labeled and stored for future use on the same patient, significant cost savings would result.

We previously examined the potential infectious consequences of collagen reuse by culturing 56 partially used collagen syringes from a single center [4]. Only one of these syringes was weakly positive for coagulase-negative staphylococcus. We could not determine whether that syringe had been contaminated during the injection process or during subsequent handling in the microbiology laboratory, and the cultures in the pilot study supported the growth of aerobic and facultative anaerobic bacteria only. These limitations prompted us to conduct a multicenter study including both aerobic and anaerobic cultures.

Materials and Methods

Between April 1999 and April 2001, partially used syringes of injectable collagen used at four centers for office-based treatment of stress incontinence were saved for this study. A total of 166 syringes were collected from the four centers. During the injection sessions only the surgeon and assistant handled the syringes, which were removed from the refrigerator immediately before use. Sterile technique was used throughout each injection session.

Two centers (the University of Louisville Health Sciences Center and the Evanston Continence Center) employed the periurethral injection technique. With the patient in the lithotomy position, the urethral meatus was prepared with povidone-iodine solution, and 3 ml of 2% xylocaine jelly were instilled into the urethra. A 1% lidocaine solution was then injected to anesthetize the length of the urethra at the 3 and 9 o'clock positions. The assistant attached a 22 gauge spinal needle to the 2.5 ml collagen syringe. This needle was inserted periurethrally and then advanced suburothelially under direct urethroscopic control of the level of the bladder neck. With the bevel of the spinal needle oriented toward the urethral lumen collagen was injected superficially, with resultant bulging of the urothelium medially into the lumen of the urethra. To avoid contamination of the material in the syringe, only positive pressure was applied to the syringe during injection. The initial injections were usually performed at the 4 and 8 o'clock positions until urethral lumen coaptation was visually confirmed. When the injection was complete, the spinal needle was removed from the syringe and the assistant recapped the syringe with its rubber stopper. No other special handling techniques were employed. The syringes were then labeled and refrigerated again within 5 minutes of use.

The other two centers (Cleveland Clinic Foundation and Greater Baltimore Medical Center) used the transurethral injection technique. The urethra was prepared with povidone-iodine as described above. The injection needle was prefilled with 0.4 ml of 1% lidocaine and then attached to the collagen syringe. The endoscope was placed at the midurethra and the needle advanced in the 3 o'clock position. The needle was then inserted under direct visualization immediately beyond the midurethra and advanced proximally to the level of the bladder neck. The collagen was then injected until the resultant mucosal bleb reached the midline. The needle was then withdrawn while positive pressure was maintained on the syringe. The needle was then removed from the collagen syringe and flushed with 1% lidocaine until it was clear. It was then repositioned in the 9 o'clock position. The material was again injected until coaptation was achieved. The partially used syringes were then labeled and stored as described above. Only syringes containing more than or equal to 0.5 ml of leftover collagen were saved for the study.

All cultures for this study were performed in the Evanston Hospital Microbiology Laboratory in one session. The culturing methods for this study were identical to those of the pilot study [4]. Syringes from the other centers were sent to this laboratory for that culturing session via overnight mail. Syringes were sent in standard envelopes without cold storage. The mean time from injection to the culturing session was 58 weeks (range 1–104 $\pm$ 23.6). None of the syringes was beyond its original expiry date at the time of culture. The first step in the culturing process was to remove the syringe cap, attach a sterile needle and draw up non-bacteriostatic saline solution into the partially used collagen syringe. The volume of collagen left over in these syringes varied, so a variable amount of saline was drawn into each syringe: the total amount of the resultant saline/collagen solution was 2 ml per syringe. Approximately 1 ml of material from each syringe was inoculated into an aerobic blood culture bottle (BACTEC Plus aerobic F, Becton Dickinson and Co., Sparks, MD) and incubated at 35°C for 5 days. In addition, 0.5 ml of material from each syringe was inoculated on to a chocolate agar plate and incubated at 22°C for 5 days. The remaining 0.5 ml of material was inoculated into a 5% sheep blood agar plate and incubated at 35°C under anaerobic conditions for 5 days.

Broth culture was qualitative in nature to identify the presence or absence and type of aerobic bacteria, but not colony count. Chocolate agar cultures identified not only type of bacteria, but also colony count. The anaerobic cultures were able to provide only presence or absence and type of bacteria.

Based on an assumption that all unopened syringes are sterile, we calculated the 'absolute risk increase' (ARI) [5] of an adverse outcome (namely local infection) associated with reusing collagen syringes during a subsequent injection session in a given patient. The ARI was calculated by taking the absolute value of the difference between the assumed infection rate (calculated below) associated with collagen reuse and the background infection rate (0.29%) [6]. The statistic 'number needed to harm' (NNH) was used to determine the number of syringes a practitioner would have to reuse before he or she would cause an infection by doing

so. NNH is calculated by taking the reciprocal of the ARI [5].

Results

One syringe from the Cleveland Clinic Fondation site was positive for >100 000 colonies of *E. coli*. This contaminated syringe had been stored for 22 weeks prior to the culturing session and was shipped to the microbiology laboratory without refrigeration (as were all other syringes from Louisville, Cleveland and Baltimore). All other aerobic and anaerobic cultures from the 166 partially used syringes were negative (0.6% were positive).

Between this study and the pilot study, a total of 222 partially used syringes were cultured and only two (0.9%) were positive. This rate was used to calculate the assumed infection rate associated with reusing collagen syringes in the following manner:

[(2 contaminated syringes)(assumed 100% infection rate) + (220 non-contaminated syringes)(0.29% infection rate)^{6}]/222 total syringes = 1.19%

The ARI (i.e. the absolute value of the difference between the two infection rates) was 0.009, and the NNH (i.e. the reciprocal of the ARI) was 111. Thus we found that a practitioner would have to reuse approximately 111 different syringes before doing so would cause a single local infection.

By multiplying 111 by the cost of a collagen syringe ($315), we found that reusing syringes would result in cost savings of $34,965 for each local infection produced.

Discussion

Glutaraldehyde cross-linked collagen is a popular, safe and effective periurethral bulking agent for treating genuine stress incontinence primarily due to intrinsic sphincter deficiency without urethral hypermobility. This material is available commercially only in 2.5 ml increments and has a shelf-life of 36 months when stored properly at standard refrigeration temperatures. Although prolonged storage at room temperature decreases the half-life of injectible collagen [6] we believe that only one or two brief exposures to room temperature do not affect the material's integrity when all such handling is done before the last day of the labeled expiry month. However, to our knowledge no literature exists regarding the integrity of this material following room temperature exposure and repeat refrigeration.

A comprehensive MEDLINE search failed to identify any reports of systemic infections associated with collagen injections, therefore we assumed that the only adverse event associated with reinjection of collagen would be local infection (i.e. periurethral abcess). In order to simplify our study design, we did not attempt to define the background local infection rate associated with collagen injection at the four centers participating in this study. Therefore, we used the local infection rate provided in the product information [6]. We did not keep up with the total number of collagen injections performed at the four centers during the study period, because we felt the relevance of that information did not justify the work associated with collecting it.

In an attempt to make this study clinically relevant, no specialized handling techniques were employed at any of the centers during the treatment sessions. The assistants simply placed the syringe caps on a shelf in the treatment rooms and then put them back on the partially used syringes immediately after injection. No viral cultures were performed for this study. We assumed that reinjecting a given patient with material from a syringe previously used on her would not increase that patient's risk of viral infection. Of course a failsafe protocol would have to be employed to ensure that only a given patient's own syringe was used for her subsequent injection sessions.

Local infection risk associated with the reuse of collagen syringes could possibly be decreased by administering prophylactic oral antibiotics at the time of injection, and through a policy of never injecting immunocompromised patients.

Conclusion

Based on the results of this multicenter study, the risk associated with storing partially used syringes of collagen for a given patient's subsequent injections is minimal. A practitioner would have to actually reuse 111 syringes (regardless of the number that he/she had saved) before this practice would cause a single local infection, and doing so would result in cost savings of $34,965 for each local infection produced. As long as a sterile technique is employed during the injection sessions and a strict labeling protocol is maintained thereafter, collagen reuse may represent a safe and cost-effective practice.

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EDITORIAL COMMENT: This is a very interesting study that demonstrates quite clearly that partially used collagen syringes maintain their sterility for long periods of time. This paper points out that, if properly handled, reinjection of a partially used syringe into the same patient may be acceptable. This would obviously require excellent sterile techniques in handling the syringes and in packing them for use at a future date. I think most practitioners should be very careful and not use these results as a license to save collagen syringes for future injections unless they are prepared to be very conscientious with their storage and handling.

Review of Current Literature

Anterior or Posterior Sacrospinous Vaginal Vault Suspension: Long-term Anatomic and Functional Evaluation

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Anterior suspensions ($n = 76$) were performed by perforation of the right retropubic space and dissection of the ipsilateral paravaginal space from bladder neck to ischial spine. Posterior suspensions ($n = 92$) was performed in the usual fashion by blunt dissection of the right rectal pillar and pararectal space. Two polytetrafluoroethylene sutures were used in all cases to anchor the undersurface of the vaginal cuff. Patients were examined postoperatively by POP-Q (pelvic organ prolapse quantification system) and a visual analog symptom questionnaire completed at the office. The anterior suspension group had a vaginal length of 9.08 cm, 0.76 cm longer than in the posterior group. The vaginal apex at straining was supported 1.91 cm higher with the anterior suspension. The anterior vaginal wall was also supported better with the anterior suspension by 0.92 cm. The posterior vaginal wall was slightly better supported by the posterior approach. Reoperation was more common in the posterior group.

Comment

The surgeries were performed at different times, rather than in a randomized fashion, and this was discussed by the authors. Although measurements are statistically significant, the clinical significance remains uncertain. However, many investigators have noted the high rate of cystocele formation or persistence after posterior vaginal vault suspension. A confirmatory study by another group would be helpful in exploring some of these questions.