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Original Article

Gender effect on dextranomer hyaluronic acid injection material durability: A rat bladder model

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ABSTRACT

Objective: In failed cases treated with the endoscopic sub-ureteric injection method, no residue from the previous injection material was found during cystoscopy at the second injection. The clinical observation of an increased incidence of recurrent reflux in girls than in boys reminds us that bladder gender may influence the stability of the injection material. The aim of the study was to determine whether there is a gender-related difference in the durability of the subureteric injection material.

Material and Methods: Twenty male and female Wistar-Albino rats were evenly divided into four groups. The experimental group received a submucosal injection of 0.1cc dextranomer hyaluronic acid copolymer (Dexell®) into the bladder. In addition, the control group received 0.1cc of 0.9% NaCl. Tissue hyaluronidase activity was measured biochemically using the ELISA method. The injection sites were assessed histopathologically and immunohistochemically with CD31 and CD34 Rabbit Monoclonal Antibodies.

Results: Biochemically, tissue hyaluronidase activity in female groups was statistically significantly higher than in males. Histopathologically, there were no significant differences between the genders or between the experimental and control groups in relation to fibrosis formation. Regarding immunohistochemistry, angiogenesis was statistically significantly higher in all females, regardless of whether they were in the study or control group, compared to males. Concerning progenitor cell activity, there is no difference between the genders, whereas the difference between the study and control groups was significant.

Conclusion: Biochemically, higher hyaluronidase activity in the female rat bladder may cause a faster breakdown of the hyaluronic acid compound in the injection material. The high permeability of inflammatory cells in the female rat bladder, as detected histochemically, may accelerate the destruction process with the aid of lytic enzymes in these cells.

Keywords: Bladder, children, gender, vesicoureteral reflux

Introduction

The incidence of VUR in children is 1-2% (1,2). Approximately 30-50% of febrile urinary tract infections in children are due to VUR. Early and accurate identification of VUR may prevent urinary tract infections and related reflux nephropathy (3).

In 2017, the American Urology Association (AUA) updated primary VUR management in children and created follow-up and treatment guidelines (4). Treatment principles can be organised into three sub-headings. Conservative options include antibiotic prophylaxis and bladder and bowel training.

Since it is minimally invasive, subureteric injection should be preferred over open surgical methods (2). However, the success rate of the endoscopic subureteric injection method depends on variables in the patient profiles, such as the degree of reflux, the techniques used, and the aptitude for the process. The average success rate ranges from 46% to 92% (5). Recurrence may be due to anatomical factors, lower urinary tract dysfunction, or the time-dependent destruction of the dextranomer hyaluronic acid (Dx-HA) compound, resulting in loss of effectiveness.

The destruction of the injection material is highly dependent on time and gender. The incidence of recurrent reflux is higher in female patients than in male patients (6). Our clinical observations also indicate gender-related differences in hyaluronic acid stability, as females demonstrate a higher incidence of recurrent reflux. In this study, we aimed to compare the stability of the active substance (Dx-HA), which may show different responses depending on gender, in male and female rats.

Materials and Methods

The study was conducted between September 2021 to November 2021 at the Gülhane Animal Surgery Research Unit, within the R&D Centre Presidency. Twenty male and 20 female Wistar Albino rats weighing 310-655 (mean: 442.5) g were kept in a standard cage, each in four groups [Group A (Female Dx-HA copolymer injection group), Group B (Male Dx-HA copolymer injection group), Group C (Female control group), and Group D (Male control group)], and were fed ad libitum. The sample size was reduced from 40 to 33 owing to losses associated with anaesthesia.

Surgical technique, injection of tissue materials, and excision of tissues

The bladder was exposed by a midline abdominal incision under general anaesthesia with intramuscular Ketamine (90 mg/ kg) and Xylazine (10 mg/kg). The bladder was incised from bladder dome to the neck, and 0.1 ml of Dx-HA copolymer was injected (26-gauge Botox needle) into the trigone submucosally in groups A and B, while 0.1 ml of 0.9% NaCl was injected into groups C and D. A 6/0 silk marker stitch was placed on the bladder mucosa near the injection area (Figure 1). The bladder was then closed with a continuous 6/0 Vicryl stitch. All groups of rats were explored again 60 days after the first procedure. The entire bladder thickness (0.3x0.3 cm) containing the injection site was excised and fixed in a 10% formaldehyde solution for histopathological sampling. To measure the tissue hyaluronidase activity biochemically, the bladder tissue was immediately prepared, frozen in liquid nitrogen, and sent for biochemical analysis.

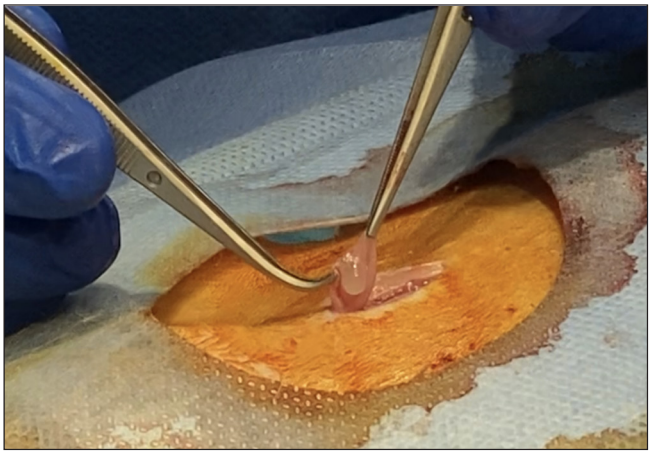

Figure 1: Injection of Dx-HA under the mucosa of the bladder wall

Histopathological evaluations

Inflammation in Hematoxylin-Eosin (H&E) stained cells and fibrosis grading was performed on Masson's trichrome-stained sections histochemically (7–9). The lymphoplasmacytic inflammatory cells, particularly the plasma cells, were counted in a large magnification field. In this context, Grade 0 indicated an absence of reaction and inflammatory cells, with no fibrosis present. In Grade 1, reactions were characterised by a maximum of 20 inflammatory cells and mild fibrosis. Grade 2 was found to correspond to moderate reactions, as indicated by the presence of 20–45 inflammatory cells and moderate fibrosis. The presence of ≥45 inflammatory cells and severe fibrosis was indicative of a Grade 3 inflammation..

Immunohistochemically, CD31 and CD34 activity were measured. Angiogenesis (number of newly formed vessels) in CD31 blocks and angioprogenitor cells in CD34 blocks were counted in the area (0.237 mm^2) where vessel proliferation is most intense under microscopic magnifications (Nikon ECLIPSE 80i microscope) (11,12). All histopathological and immunohistochemical examinations were carried out in a blinded manner by independent observers.

Rat tissue hyaluronidase measurement:

Tissue samples were stored in a deep freezer (Sanyo MDF-U6086S) at -80 C^0 until analysis. On the study day, excess blood on the tissues was removed in cold PBS (Phosphate Buffer Saline) (pH 7.4). Tissue protein measurements were performed with tissue hyaluronidase from the supernatants separated after centrifugation. Tissue hyaluronidase measurements were done with an enzyme-linked immunosorbent assay method with the original kit for Rat Hyaluronidase of BT LAB (Bioassay Technology Laboratory- Shanghai Korain) in Cobas c501 Roche Hitachi device, turbidimetrically with the Benzethonium chloride method. The tissue hyaluronidase results were calculated as ng/mg protein according to the measured proteins of the homogenates.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). The study included eight variables in total, five of which were defined as dependent variables (fibrosis grade, inflammation grade, anti-CD31 expression, anti-CD34 expression, and tissue hyaluronidase level). Gender and injection-material group membership were treated as independent variables. The normality of continuous variables was assessed using visual inspection of histograms together with skewness and kurtosis values. Descriptive statistics for normally distributed continuous variables were reported as mean and standard deviation (SD). Categorical variables

were expressed as frequencies (n) and percentages (%). Group comparisons for normally distributed continuous variables were performed using the Independent samples T test. Comparation of categorical variables were assessed using the Pearson chi-square test. A two-tailed p-value of <0.050 was considered statistically significant.

Results

Tissue hyaluronidase activity in female rats is higher than in male rats, irrespective of study vs. control groups (Male vs. female; 26.85±11.06 vs. 45.84±14.95; p<0.001) (Control vs. study; 38.69±18.77 vs. 36.93±14.15; p=0.618) (Table I-II).

In the examination performed with H&E dye, microspheres filled with biomaterial and degraded (empty) microspheres were observed together in the area of the injection material in the male and female study groups. At the same time, the honeycomb appearance is kept in the microspheres of the biomaterials whose content has been degraded. Plasma cells, neutrophils, eosinophils, macrophages, and mast cells were present in the area of inflammation, with a predominance of lymphocytes around the injection material. Multinucleated giant cells and foreign body reactions were observed among the injection materials. The capsule material formed by fibroblast and collagen fibres was kept to surround the area from the outside. Significant inflammation was observed in the Dx-HA-injected male and female study groups. Foreign body reaction, microsphere formation, or inflammatory processes were not observed in the control groups (Figure 2: A/E/I/M).

In the preparations stained with hematoxylin-eosin, lymphoplasmacytic inflammatory cells, particularly plasma cells, were counted under magnification (x40) in a High Power Field (HPF). The counts of inflammatory cells were significantly higher in the study group compared to the control group (30.40±24.18 vs 5.81±7.98; p<0.001) (Table II). However, no statistically significant difference was observed in inflammatory cell counts between males and females (16.41±15.53 vs 22.21±27.17; p= 0.301).

In the histopathological examination with Masson Trichrome stain to evaluate fibrosis, microspheres filled with biomaterial and degraded microspheres were observed together, in correlation with Hematoxylin-eosin staining in the area where the injection material was present in the male and female study groups. The capsule formed by fibroblast and collagen fibres surrounded the Dx-HA copolymer from the outside (Figure 2: B/F/J/N). In line with these data, fibrosis was graded by looking at the degree of collagenisation and fibroblastic proliferation rate per HPF(x40). There was no statistically significant difference between the study and control groups, regardless of gender (p =0.123). Fibrosis

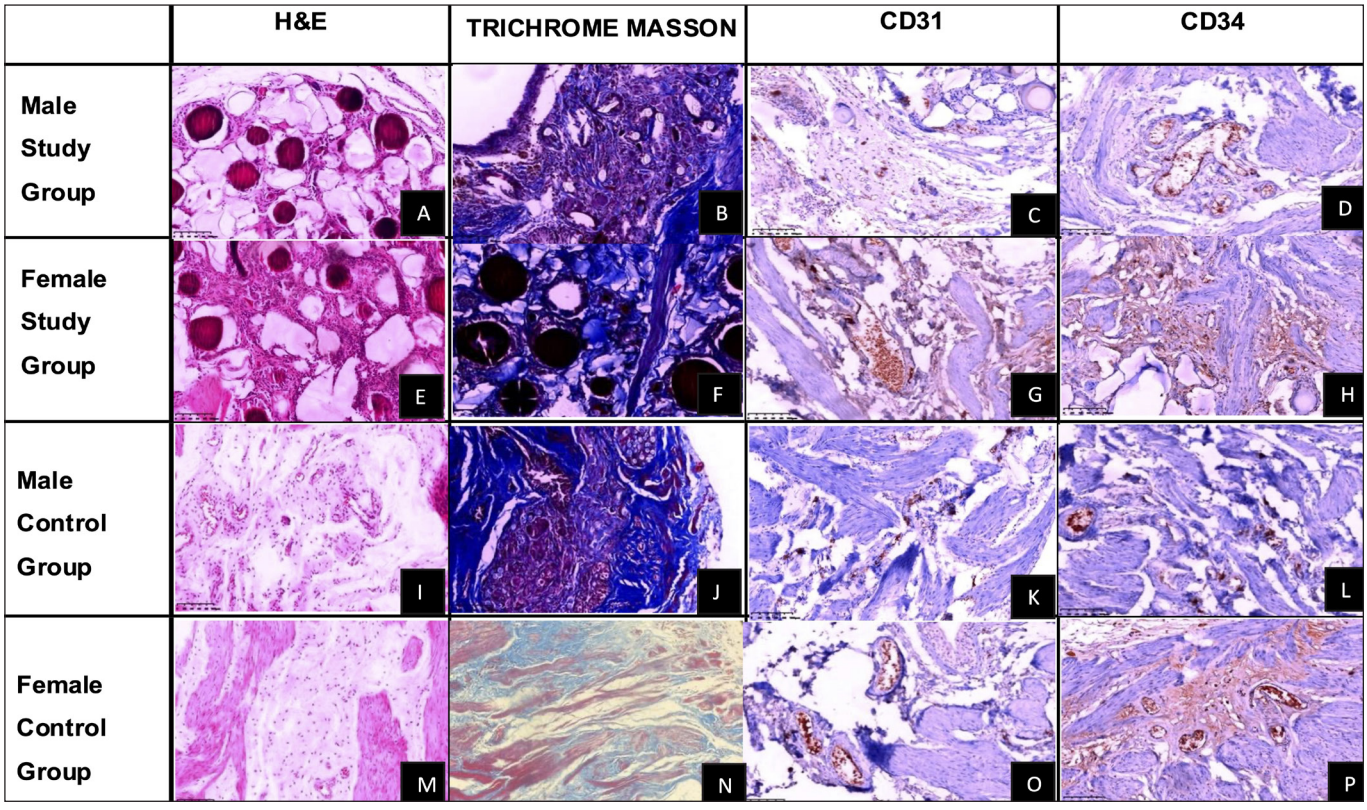

Figure 2: Evaluation of histopathological findings. Preparations stained with H&E **(A)**, and Masson Trichrome **(B)**, CD31 (C), and CD34 **(D)** in the male study group; Preparations stained with H&E **(E)**, and Masson Trichrome **(F)**, CD31 **(G)**, and CD34 **(H)** in the female study group; Preparations stained with H&E **(I)**, and Masson Trichrome **(J)**, CD31 **(K)**, and CD34 **(L)** in the male control group; Preparations stained with H&E **(M)**, and Masson Trichrome **(N)**, CD31 **(O)**, and CD34 **(P)** in the female control group.

Table I: Comparison of hyaluronidase enzyme activity between gender and test groups

Groups	Control	Study	p†	Total	p‡
Male					
n	7	7	0.328	14	<0.001
HA*	28.80±12.63	24.91±9.83		26.85±11.06	
Female					
n	9	10	0.571	19	<0.001
HA*	46.38±19.73	45.36±11.01		45.84±14.95	
Total					
n	16	17	0.328	33	-
HA*	38.69±18.77	36.93±14.15		37.78±16.31	

***:** *mean±SD,* **†:** *Control vs. Experimental (Independent Samples T-Test),* **‡:** *Male vs. Female (Independent Samples T-Test),* ***HA:** Hyaluronidase enzyme activity*

Table III: Comparison of inflammation, fibrosis, CD31 and CD34 cell counts between gender and test groups

	Group difference			Gender difference		
	Control	Study	p	Male	Female	p
Inflamatory cells*	5.81 ± 7.977	30.40 ± 24.184	<0.001	16.41 ± 15.528	22.21 ± 27.168	0.301
Fibrosis†	16 (44.44%)	20 (55.55%)	0.123	17 (47.22%)	19 (52.77%)	0.200
CD31⁺ cells*	8.12 ± 3.845	16.40 ± 8.357	<0.001	10.41 ± 8.689	14.79 ± 6.571	0.035
CD34⁺ cells*	9.81 ± 3.468	18.30 ± 7.766	0.002	13.41 ± 11.017	15.53 ± 6.013	0.282

***:** *mean±SD (Independent samples t-test),* **†:** *n(%) (Pearson's chi-squared test)*

scores were similar between male and female rats (1.24±0.75 vs. 1.53±0.70; p =0.200), and likewise comparable between the study and control groups (1.16±0.76 vs. 1.19 ± 0.66; p=0.123) (Table II).

In the CD31-stained sections, the endothelial cell counts were significantly higher in the study group compared with the control group (16.40±8.36 vs. 8.12±3.84; p<0.001). Additionally, irrespective of study or control status, females exhibited higher endothelial cell counts than males (14.79±6.57 vs. 10.41±8.69; p=0.035).

In CD34 antibody-stained preparations, angioprogenitor cells listed in the vascular trace showed a statistically significant difference in the direction of the study group (Study vs. Control; 18.30±7.77 vs. 9.81±3.47; p=0.002) (Table II). There was no statistically significant difference in gender (Male vs. Female; 13.41±11.02 vs. 15.53± 6.01; p = 0.282).

Discussion

The endoscopic treatment method is a minimally invasive procedure and is an excellent alternative to early discontinuation of antibiotic prophylaxis and open surgical approaches. While the average success rate varies between 76-92%, the failure rate after injection changes 5-25%. Furthermore, it is important to note that numerous factors can influence the efficacy of treatment. The following factors must be considered: the type and volume of injected material, the technique applied, the surgeon's experience, the degree of reflux detected, the presence of bilateral or unilateral reflux, voiding dysfunction, age, and gender(13–15). Consistent with our clinical observations, it was also found in the literature that the recurrence rate was higher in girls who underwent endoscopic injections for VUR (16). Endoscopic injection failure was higher in children younger than 54 months, children with previously failed injections, and girls (17,18).

HYAL-1 is a bladder-specific hyaluronic acid in the extracellular matrix (19,20). Pseudocapsule formation at the injection site suggests that the mechanism of action of Dx-HA involves an early inflammatory response (21). Injection materials used in treating SI cause a foreign body reaction and form a capsule consisting of fibroblast and collagen (22). What we expect from an ideal subureteric injection material is that it provides capsule formation and maintains the mass effect. Studies have shown that only 20% of the injection material persists one year after the procedure. Capsule formation was also observed around the degraded materials, and it was observed that the mass effect continued (22).

The dextranomer molecules contained in the injection material are responsible for the adhesion of the filler material to the tissue. In our study, regardless of the study and control group, statistically significantly higher tissue hyaluronidase activity was found in female rats than in male rats (p<0.001). This finding may cause faster destruction of hyaluronic acid in female rat bladders than in male rats. As a result, it may lead to a reduction in the mass effect of the dextranomer structure in the Dx-HA complex (19,20).

Our study is the first to discuss that tissue hyaluronidase activity and injection material stability may differ due to bladder gender.

In our study, when H&E stained preparations were examined, mononuclear cell migration, mainly lymphocyte, around the microspheres filled with Dx-HA in the bladder submucosa was observed in the study groups. The control groups had no significant inflammatory cell chemotaxis to the bladder submucosa. Foreign body reaction was observed with multinucleated giant cells among the injection materials. The capsule formed by fibroblast and collagen fibres was observed to surround the Dx-HA-filled microsphere from the outside, and findings similar to the study by Kajbafzadeh et al. (23) were obtained. As a result, in our study, there was a significant difference between the study group and the control group in terms of the inflammatory response ($p<0.001$). However, no significant differences were found in the contribution of the gender to the inflammatory process ($p=0.301$). The Dx-HA complex injected into the body induces a foreign body reaction, promoting the migration of all mononuclear cells to the injection site. This allows a pseudo capsule to form around the injection material over the long term. Consequently, the activity of the hyaluronidase enzyme found in the bladder degrades the binding agent hyaluronic acid in the Dx-HA complex, decreasing the effectiveness of the injection material. However, it was noted that there was no statistical difference between male and females regarding this reaction that would cause the inflammatory cell response of mononuclear cell migration to differ.

An ideal injection material in endoscopic treatment should not provoke a long-term chronic inflammatory process, as a sustained inflammatory response can lead to fibrosis. Our study found that the inflammatory process was managed by encapsulating the material created by fibroblasts and collagen fibres, as observed in preparations stained with Trichrome-Masson. To evaluate this response, we graded fibrosis by assessing the degree of collagenisation and fibroblast proliferation rate. Our study indicated no statistically significant difference regarding fibrosis between the study and control groups nor between the genders ($p=0.123$). The evaluation was conducted two months post-injection. The absence of fibrosis suggests that the Dx-HA complex is a suitable biomaterial for biocompatibility.

Inflammatory angiogenesis occurs at more excellent rates in females. In the Dx-HA group, female rats demonstrated a higher proliferation of vascular endothelial cells and inflammatory angiogenesis than male rats. The reduced angiogenesis activity in male rats may allow the injected material to remain stable for a longer duration. This suggests that HA may experience a more rapid inflammatory response in females and, consequently, may remain stable for a shorter period. This finding indicates that the stabilisation time of the Dx-HA complex may vary based on gender.

In our study to determine microvessel density using the anti-CD34 antibody against CD34, an endothelial marker, we assessed angioprogenitor cells in the most remarkable vascular proliferation region. There was no significant difference between the gender in this evaluation ($p=0.282$); however, a notable difference was observed between the study and control groups regarding microangiogenesis formation ($p=0.002$). The increase in CD34-positive cells may suggest that Dx-HA triggered inflammatory processes, substantially enhancing microangiogenesis. Nevertheless, gender was not a determining factor in this process. These findings support the notion that the biological stabilisation of Dx-HA may develop independently of gender but could depend on the severity of the inflammatory response.

The presence of progenitor cells at the injection site, even two months post-injection after their sacrifice, indicates that the inflammatory process remains ongoing. The existence of angioprogenitor cells in the injected area suggests that further activity enhances vascularity; consequently, inflammatory cells will migrate to the site, and the secreted cytokines will disrupt the structure of the filler, increase its breakdown, reduce the mass effect, and may trigger the recurrence of reflux, regardless of gender. While this finding aligns with the study by Kajbafzadeh et al. (23), a more extended follow-up period is recommended to evaluate the literature on the angioproliferation process secondary to inflammation using CD34 more effectively. Moreover, studies on inflammatory responses involving CD34 require an extended follow-up for subsequent evaluations to retain significance. Consequently, according to the literature, the assessments conducted in the sixth month are considered more reliable. In the short term, there is no significant difference in progenitor cell activity between male and female rats, suggesting that CD34 is a marker that should be assessed over a more extended period than CD31. This reliance on a relatively brief follow-up period represents a limitation of the present study, as it may have restricted the ability to fully capture late-phase inflammatory and regenerative processes.

Conclusion

Dx-HA is nearly an ideal material for the treatment of reflux. Since it does not induce chronic inflammation, it is unlikely to contribute to fibrosis's potential mid- and long-term development. However, biochemically, increased tissue hyaluronidase activity in female rat bladders may lead to a more rapid breakdown of hyaluronic acid within the Dx-HA complex. The elevated degradation rate adversely affects the stability of the injectable substance, which could diminish the volumetric augmentation efficacy of the bulking agent, thereby heightening the likelihood of suboptimal therapeutic outcomes. Consequently, this raises the possibility of suboptimal therapeutic outcomes.

Clinically, we have observed that recurrence following subureteric injection is more common in females than in males, as supported by the existing literature. Our study proposes that this may be attributed to the increased vascularity and activation of hyaluronidase in female bladders. Therefore, it should be considered that subureteric

injections administered to females will degrade more rapidly. We suggest that a larger volume be administered compared to males. Additionally, scheduling follow-up appointments for girls more frequently than for boys after the procedure may be beneficial.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Health Sciences University Gulhane institutional (02.09.2021, reference number: 2021-28).

Contribution of the authors

Concept or design: IS, SEUB, Acquisition of data: SEUB, GŞ, SD, Analysis or interpretation of data: SEUB, PS, Drafting of the article: SEUB, GBB, IS, Critical revision for important intellectual content: IS, HS, SD

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Conflict of interest

The authors declare that there is no conflict of interest.

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