Original Article

Anti-adhesion agent to prevent of post-operative adhesion and fibrosis after vasectomy: a study using a rat model

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Background: Post-vasectomy pain syndrome (PVPS) is difficult to treat. Direct damage to the vas deferens, inflammation, compression of nerves through fibrotic adhesions, and congestion of the epididymis are known to cause PVPS. The purpose of this study was to evaluate whether the application of anti-adhesion agents after vasectomy can reduce the degree of adhesion and fibrosis in a rat model.

Methods: In the study, 11 Sprague-Dawley rats (22 vas deferens) from each group were evaluated. In the experimental group, surgery was terminated after applying the anti-adhesion agent; this was not applied in the control group. After 14 days of vasectomy, the scrotum was dissected to evaluate the degree of gross adhesion at the vasectomy site. Histological examination of the surrounding tissues, including the vas deferens and the spermatic cord, was also performed.

Results: Adhesions were not observed in 72.73% (16/22) rats from the experimental group, in which the anti-adhesion agent was applied; in contrast, the incidence of adhesions in the control group was 100%. There was a statistically significant relationship between the distribution of grades for adhesion and anti-adhesion agent (chi-square, P<0.001). On classification of fibrosis and inflammation, application of the anti-adhesion agent was significantly associated with lower grade inflammation and fibrosis compared to that of the control group (chi-square, P=0.001). The rate of intact muscle structure was 90.91% (20/22) in the experimental group, and 36.36% (8/22) in the control group, and the application of the anti-adhesion agent demonstrated significant association with preservation of intact muscle structure (chi-square, P<0.001).

Conclusions: The application of an anti-adhesion agent after vasectomy prevented the development of adhesion, fibrosis, and inflammation reaction and further reduced structural destruction.

Keywords: Vasectomy; pain; syndrome; fibrosis

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Introduction

Vasectomy is the most effective and considerably common contraceptive surgery with a 98% success rate (1). However, chronic scrotal pain develops after vasectomy in certain cases; this is known as the post-vasectomy pain syndrome (PVPS) (2). PVPS is a typical late complication of vasectomy, that can be diagnosed when persistent or intermittent scrotal pain lasts for more than three months after a vasectomy (3).

The etiology or mechanism of PVPS has not been clearly identified. However, similar histological features including a thickened basement membrane, degeneration of the spermatic cord, perineural fibrosis, and adhesions can be confirmed in patients with PVPS (4). This syndrome is caused by direct damage to the vas deferens, inflammation, nerve compression through fibrotic adhesion, and congestion of the epididymis (5). Immunological factors mediated through the formation of anti-sperm antibodies, which are produced when sperm are exposed, may affect inflammatory reaction (6). Serum anti-sperm antibodies are detected in 60–80% of men after the blood-testis barrier is destroyed during vasectomy (7). These antibodies have been shown to elicit an organized immune response in animal models (8). Hattikudur *et al.* reported that the incidence of agglutinating antibodies rises to 60% by 4 years post-vasectomy and reaching 76% in 6–8 years (9). It has also been suggested that pain occurred from inflammation with extravasation of spermatozoa around the epididymal tubules and at the site of vasectomy (7). These mechanisms may work independently or in combination, ultimately leading to testicular or epididymal pain after vasectomy.

There has been no research on the prevention of PVPS. Among the various causative factors, adhesions and fibrosis are the factors that can be controlled by the surgeon during vasectomy. In order to prevent post-operative adhesion and fibrosis, which are caused from the inflammatory reaction, it is required to achieve the precise dissection of the vas deferens as well as the aseptic techniques, and the appropriate usage of antibiotics and anti-inflammatory drugs might be prescribed if needed. In addition, the application of anti-adhesion agents, which are currently widely used in clinical practice, can be considered. Chung *et al.* reported that persistent pain after epididymectomy for chronic epididymitis was effectively prevented by using an anti-adhesion agent. They suggested that the cause of the persistent pain after epididymectomy, which is perineural and interstitial fibrosis, is may similar to that of PVPS (10). However, studies have not been conducted on the effectiveness of the application of anti-adhesion agents during vasectomy. In this study, the effect of an anti-adhesion agent, applied between the vas deferens and surrounding tissues after vasectomy, on the inhibition of adhesions and fibrosis and the preservation of muscle structure was histologically evaluated in a rat model. We present the following article in accordance with the ARRIVE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-21-1170/rc).

Methods

Study design

Overall, 24 male Sprague-Dawley rat were housed. Among them, a preliminary experiment was conducted on two rats to evaluate the uniformity of the surgical and experimental methods and the stability of the operation. After one week of stabilizing the experimental animals, bilateral vasectomy was performed in 22 animals (44 vas deferens). During surgery, the anti-adhesion agent was applied to 22 vas deferens in the experimental group; the operation was terminated without application of the agent in the control group. Two weeks after vasectomy, autopsy was performed and 44 specimens were collected. During autopsy, the degree of gross adhesion was evaluated, and the collected specimen was fixed in formalin for two days. After fixation, paraffin blocks and slides were prepared and stained to proceed with histological examination.

During the stabilization period, 12-week-old male Sprague-Dawley rats (weighing 250–300 g) were reared in cages for 1 week. After vasectomy, each animal was kept in an individual cage; purified drinking water and feed were provided for free feeding, and the room temperature was maintained at 22±1 ℃. The light source was turned on from 7 am to 7 pm in both control and experimental groups, and the light source was blocked from 7 pm to 7 am.

Anti-adhesion agent

The used anti-adhesion agent (MEDICLORE®, CG Bio Co., Ltd., Korea) was a mixture of a highly biocompatible water-soluble mucoadhesive polymer (Poloxamer 188/407) with chitosan, and gelatin, that was capable of temperature-dependent sol-gel transfer. This agent is widely used in the current clinical field (11,12). It exists as a solution at room temperature and becomes a highly viscous gel at body

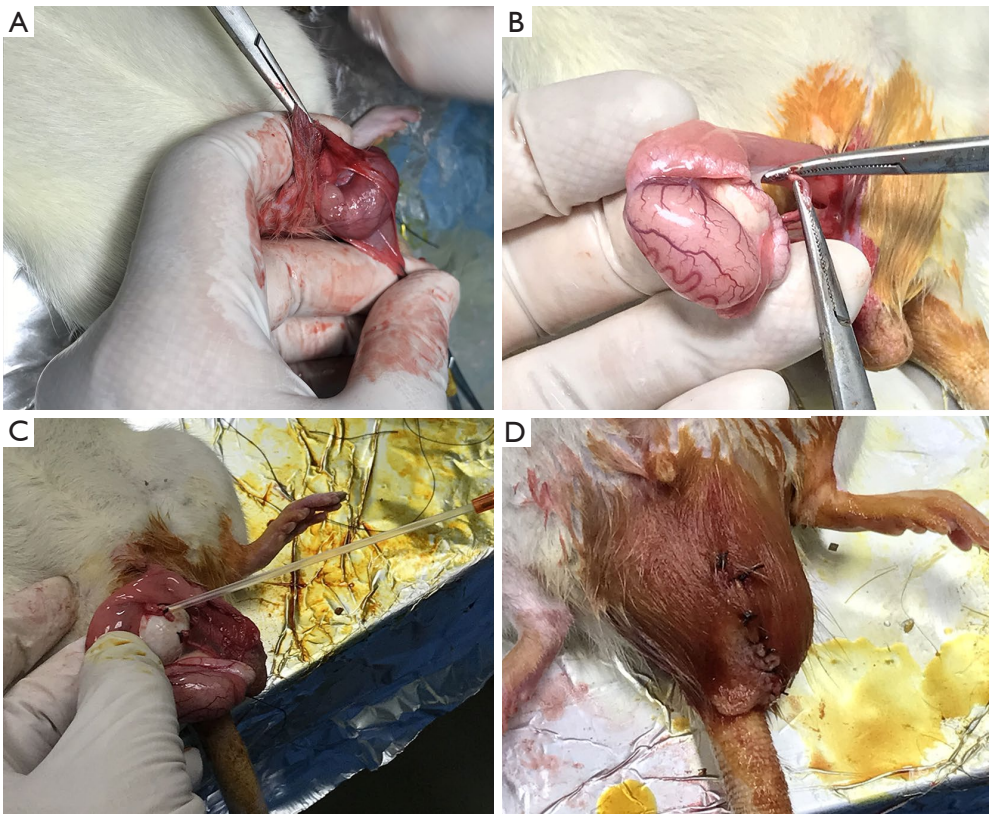

Figure 1 The process of vasectomy. (A) Dissection of the spermatic cord and exposure of the testis, epididymis, and vas deferens. (B) Clamping of the vas deference using hemostatic mosquito forceps. (C) Application of anti-adhesion agent at the vasectomy site. (D) Skin closure by interrupted sutures.

temperature, acting as a physical barrier. This physical barrier prevents tissues from sticking together during the wound healing process.

Anesthesia and vasectomy

Inhalation anesthesia with isoflurane was used; a mixture of oxygen (55 psi & 500 cc/min) and isoflurane was used at a concentration of 2.5–3% for anesthesia. After draping and dressing the scrotum with povidone iodine, a 1–2 cm vertical midline incision was placed in the scrotum. The testis and spermatic cord were then exposed by incising the tunica vaginalis. After incising the exposed spermatic cord, the vas deferens was dissected using hemostatic mosquito forceps and Metzenbaum scissors. Grasping both sides of the vas deferens with hemostatic mosquito forceps, the vas deferens was resected using a cold knife, and both open ends were ligated with absorbable sutures. In the experimental group, an anti-adhesion agent was applied to the resected vas deferens and surrounding tissues (1–2 cc for each vas deferens); an identical procedure was performed on the contralateral side. In the control group, the scrotum was closed without applying an anti-adhesion agent (*Figure 1*).

Autopsy

After inhalation of isoflurane anesthesia, euthanasia was performed using carbon dioxide, and venesection was performed from the level of the abdominal aorta. The previous surgical site of the scrotum was resected, including the site of the vasectomy. In the case of no tissue adhesion, samples of the vas deferens, sutured sites, and adjacent tissues measuring 1 cm × 1 cm were obtained; mass resection was performed when the adhesion was severe, and the surrounding tissues were not dissected. In cases with severe adhesion, the tissue fixed on the slide measured 1 cm × 1 cm, and contained surrounding tissues including the vas deferens at the site of the vasectomy.

Gross classification for the degree of adhesion

At autopsy, the degree of adhesion was grossly determined and classified by one urologist. The degree of adhesion was classified using Mazuji's classification (13), as follows: 0: no adhesion, 1: very small, irregular adhesion, 2: easily separable medium intensity adhesion, 3: intense, not easily separable regular adhesion, and 4: very intense, not easily separable, homogenous adhesion. Metzenbaum scissors, hemostatic mosquito forceps, and smooth forceps were used for the autopsy. The degree of adhesion was confirmed by dissecting the tissues using an instrument.

Pathological classification

Each group was evaluated independently by two blinded pathologists.

Hematoxylin-Eosin stain (H&E stain) for inflammation assessment

The number of inflammatory cells was evaluated on 400× magnification. Cases where inflammatory cells were not visible were classified as having no inflammation; those with 10 or less, 11–50, 51–100, and more than 100 were classified as having minimal, mild, moderate, and severe inflammation, respectively.

Masson's trichrome stain (TRC stain) for the assessment of fibrotic change

The degree of fibrosis was classified using Ozkan's classification (14), as follows: 0: no fibrosis, 1: minor fibrosis, 2: easily observed thick fiber bands, 3: well-developed fine collagen fiber bands, and 4: a large area of significant fibrosis.

α-smooth Muscle Actin (α-SMA) staining for the assessment of structural damage

Muscular structure was classified into well-maintained and not well-maintained categories.

Statistical analysis

The chi-square test was used for categorical variables, and statistical analyses were performed using SPSS® software, version 21.0; for all two-sided tests, $P<0.05$ was considered statistically significant.

Ethical statement

Experiments were performed under a project license (No. EUIACUC 19-14) granted by the Animal Experimental Ethics Committee of Eulji University, in compliance with institutional guidelines for the care and use of animals.

Results

The degree of adhesion

On gross analysis of adhesions in the experimental group, 72.73% (16/22), 18.18% (4/22), and 9.09% (2/22) were of grade 0, 1, and 2, respectively. In the control group, 18.18% (4/22), 36.36% (8/22), 18.18% (4/22), and the remaining 27.27% (6/22) were grade 1, 2, 3, and 4 adhesions, respectively (*Table 1*, *Figure 2*).

Inflammation

Among the 22 specimens in the experimental group, 18.18% (4/22) showed no inflammation, 36.36% (8/22) showed minimal inflammation, and 45.45% (10/22) showed mild inflammation. Among 22 specimens in the control group, 27.27% (6/22), 18.18% (4/22), 22.73% (5/22), and 31.82% (7/22) showed minimal, mild, moderate, and severe inflammation, respectively (*Figure 3*, *Table 1*).

Fibrotic change

In the experimental group (n=22), 36.36% (8/22), 45.45% (10/22), and 18.18% (4/22) cases demonstrated grade 0, 1, and 2 fibrosis, respectively. Among 22 specimens of the control group, grade 0, 1, and 2 fibrosis were observed 18.18% (4/22), 9.09% (2/22), and 18.18% (4/22) cases, respectively; grades 3 and 4 were observed in 27.27% (6/22) each (*Table 1*, *Figure 4*).

Structural damage

Overall, 90.91% (20/22) of the experimental group and 36.36% (8/22) of the control group showed intact muscular structure (*Figure 5*, *Table 1*).

Safety

No events, including anti-adhesion agent related adverse events, occurred in the both groups.

Table 1 Experimental results

	Experimental group (n=22)	Control group (n=22)	P value
Gross			<0.001
Grade 0	16 (72.73%)	0	
Grade 1	4 (18.18%)	4 (18.18%)	
Grade 2	2 (9.09%)	8 (36.36%)	
Grade 3	0	4 (18.18%)	
Grade 4	0	6 (27.27%)	
Inflammation			0.001
No inflammation	4 (18.18%)	0	
Minimal	8 (36.36%)	6 (27.27%)	
Mild	10 (45.45%)	4 (18.18%)	
Moderate	0	5 (22.73%)	
Severe	0	7 (31.82%)	
Fibrosis			0.001
Grade 0	8 (36.36%)	4 (18.18%)	
Grade 1	10 (45.45%)	2 (9.09%)	
Grade 2	4 (18.18%)	4 (18.18%)	
Grade 3	0	6 (27.27%)	
Grade 4	0	6 (27.27%)	
Muscular structure			<0.001
Intact	20 (90.91%)	8 (36.36%)	
Damaged	2 (9.09%)	14 (63.63%)	

Discussion

This pre-clinical study evaluated a method that may reduce the incidence of PVPS. The present study showed that the application of an anti-adhesion agent after vasectomy effectively prevented adhesion and fibrosis around the vas deferens.

Early complications such as bleeding, hematoma, and infection occur in approximately 2% to 3% of patients after vasectomy (1). PVPS may cause negative impact on quality of life in about 1–2% of men (15). However, according to the recent systematic review, overall incidence of post-vasectomy pain is range from 9% to 25% and PVPS is range from 3% to 8% (16). This wide range in incidence of PVPS may come from the diagnosis by the subjective symptoms and vasectomy usually performs in the healthy people. Moreover, severe PVPS requires additional treatment in approximately 0.1% of vasectomy cases (7). Additional surgery such as epididymectomy, vasovasostomy, and denervation is needed to treat PVPS (17,18). These surgeries provide a satisfaction rate of 85% (19).

Vasectomy is performed in the two steps including the delivery of vas deferens and occlusion. Delivery can be achieved by the traditional incision in scrotum or by non-scalpel method. The non-scalpel technique is less invasive which reduces damage to vasculature and nerves, compared to the scalpel technique. Some studies reported that the non-scalpel technique showed superior outcomes in post-vasectomy pain than scalpel technique (20,21). However, the incidence of PVPS was not differed between the scalpel and non-scalpel vasectomy (16). The various occlusion methods have been developed including ligation, surgical clips, thermal or electrocautery, intraluminal mucosal-cautery and chemical occlusion. However, the excision and

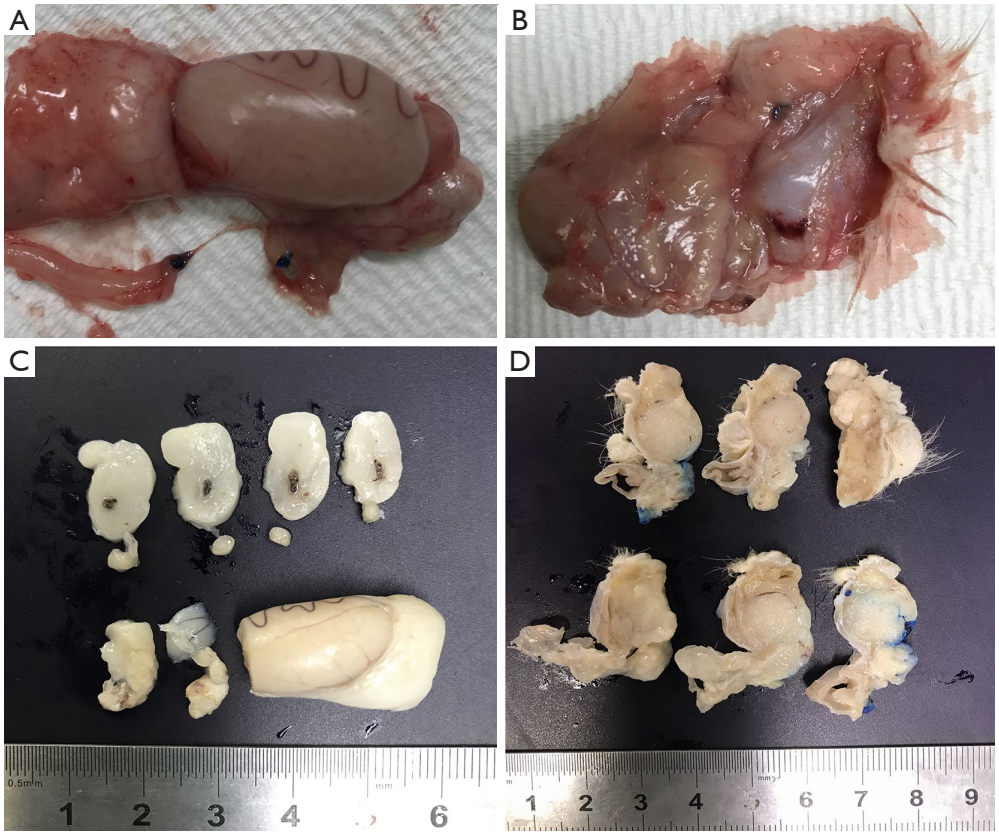

Figure 2 Representative images of gross classification for the degree of adhesion. (A,C) Experimental group: grade 0. (B,D) Control group: grade 4.

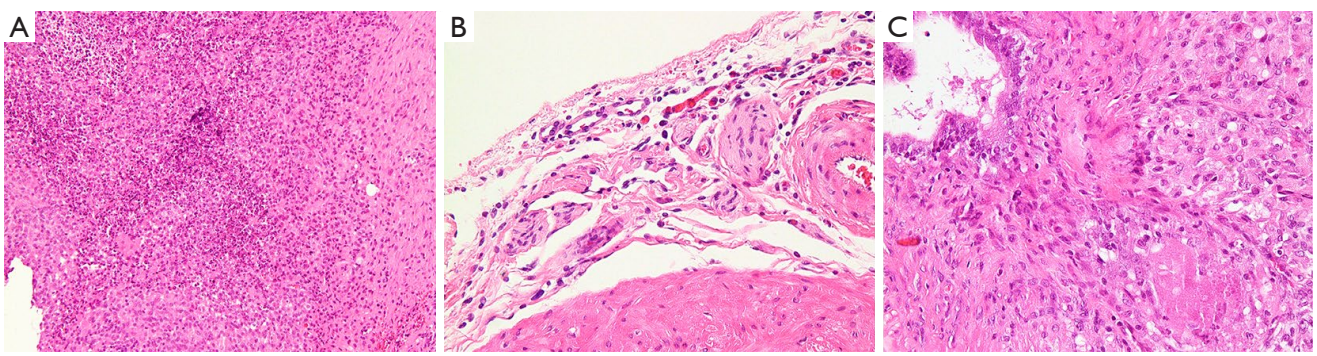

Figure 3 Hematoxylin-eosin stain for inflammation assessment. (A,B) Experimental group. (A) Granulomatous inflammation is limited at the vasectomy site. (B) Remaining vas deferens retains normal anatomy; patent lumen, circular smooth muscle, and thin adventitia observed without inflammation. (C) Control group. Compared to the experimental group, a larger extent of inflammation is observed around the remaining vas deferens. Massive granulomatous inflammation with foreign body reaction involving the entire thickness of the vas deferens. (A-C) ×400.

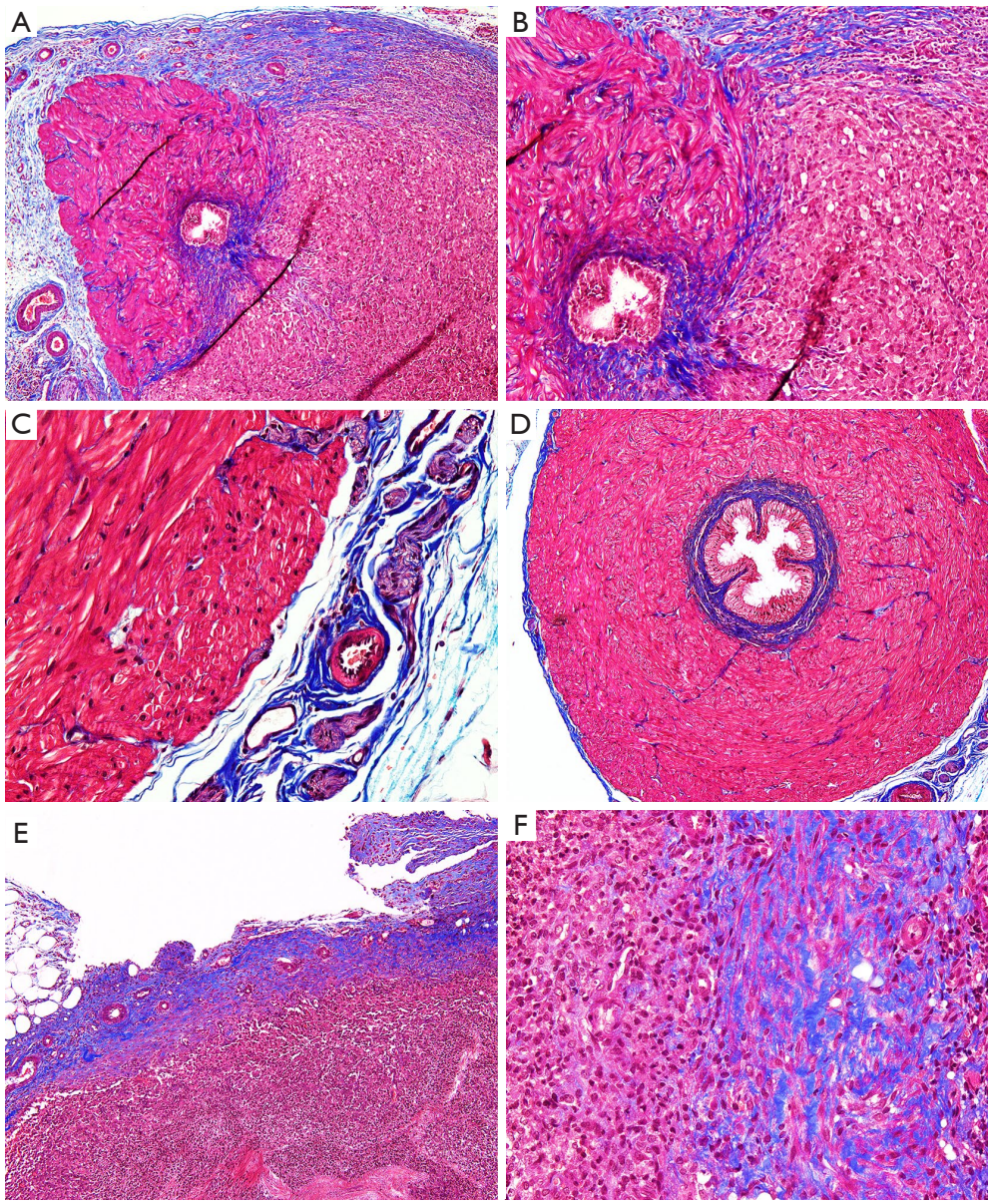

Figure 4 Masson's trichrome stain for fibrotic change assessment. (A,B) Control group. Mild interstitial fibrosis is found in the remaining muscular wall and adventitia of the vas deferens, control group (C,D). Vasectomy site and (E,F) vasectomy area of the experimental group. The experimental group shows normal vas deferens lined by ciliated columnar epithelium with thick circular smooth muscle and adventitia at the outermost part. (A,C,E) ×100, (B,D,F) ×400.

ligation is still the most widely used technique (22). In this study, the traditional method of vasectomy was performed using vertical scrotal incision with excision and ligation technique. Although it was unable to assess the effect of anti-adhesion agents in the vasectomy using other surgical techniques in this study, similar outcomes could be expected considering the mechanism of the inflammatory reaction.

The mechanism of PVPS can be explained by two hypotheses, the first being obstruction due to interstitial fibrosis and the second being perineural fibrosis (7,19). Both hypotheses suggest that fibrosis causes PVPS. Fibrosis and adhesions are inevitable results of the process of repair in inflammatory reactions; the formation of adhesions and fibrosis involves exudation, reabsorption, and recovery

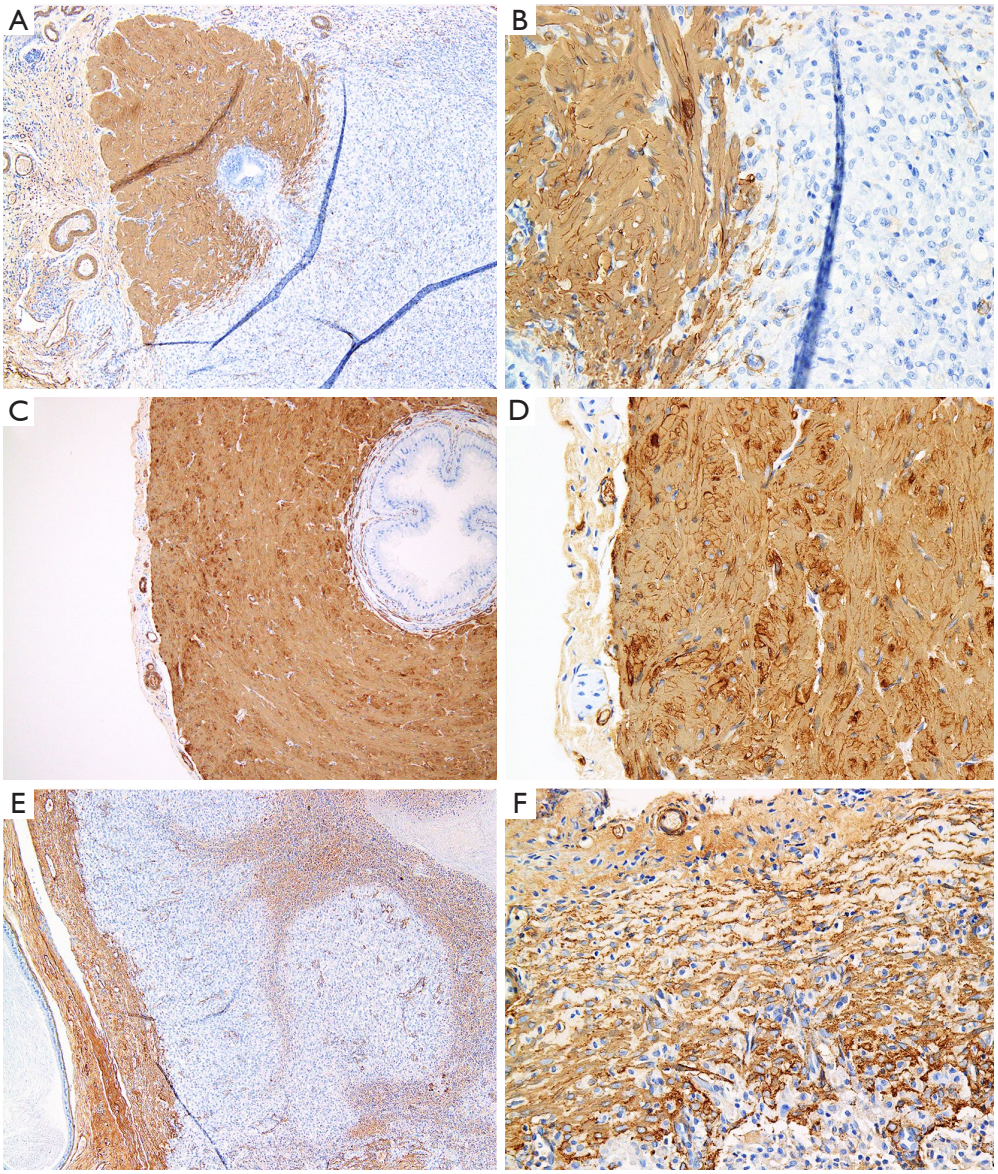

Figure 5 α-smooth muscle actin stain for the assessment of structural damage. (A,B) The muscle layer is destroyed by inflammation, control group (C,D). Vasectomy site and (E,F) vasectomy area of the experimental group. The experimental group showing normal vas deferens lined by ciliated columnar epithelium with thick circular smooth muscle. (A,C,E) ×100, (B,D,F) ×400.

phases (23). Fibrin effusion is observed from coagulated tissues during the exudation period; in the reabsorption period, granular leukocytes, monocytes, and macrophages migrate to the surgical site and fibrin lumps are formed. The recovery period extends over weeks to months after tissue injury, and granulation tissue is formed by fibroblasts (24). During this process, the inflammatory response within 24 to 36 hours after the tissue injury has the most important effect on the occurrence of adhesion and fibrosis (25). First adhesion formation within 36 hours of the inflammatory reaction is known to be an important period to determine the extent of scarring until 1 month after surgery (11). According to Shin *et al.*, anti-adhesion agent showed less inflammatory reaction and fibrosis at 4 weeks after surgery in the histological findings (26).

Anti-adhesion agents are widely used in clinical practice to prevent fibrosis and adhesion between tissues after surgery. Chung *et al.* reported that the use of anti-adhesion

agents after epididymectomy for chronic epididymitis can reduce chronic scrotal pain after surgery (10).

Natural barriers such as the peritoneum, omentum, and amniotic membrane prevent inter-tissue adhesion (27). However, when these structures are damaged by surgery using synthetic physical barriers, anti-adhesion agents are required to prevent unnecessary adhesion and fibrosis from inflammatory reactions (28). Synthetic physical barriers are available in various forms, such as films, liquids, and sol-gel preparations (29). In cases where organs are small and irregular in shape, such as in vasectomy sites, liquid or sol-gel types are appropriate as these formulations are injectable. The anti-adhesion agent used in this study is a temperature-sensitive sol-gel type product composed of poloxamer, gelatin, and chitosan. It exists as a solution at room temperature and changes to a viscous gel at body temperatures of above 28–30 ℃. Poloxamer is already widely used in the medical field, and is a triblock copolymer consisting of a central block of polypropylene glycol (PPG) flanked by two polyethylene glycol (PEG) chains (30). Poloxamer may exist as a liquid, sol, gel, or solid depending on the ratio of PEG/PPG. In addition, PPG can stay on the tissue surface for a long time because of its hydrophilic nature. Chitosan has biocompatible, biodegradable, non-toxic, and non-allergic properties (31). Chitosan has positive charge, and therefore tends to stick to the tissue surface; it is also expected to have antibacterial effects. Gelatin is also an adsorbent material that offers the advantage of retention on the tissues. Therefore, it is more effective for preventing adhesions owing to its retaining properties, which can be maintained for a long time on the surface of damaged tissues.

Fibroblasts that proliferate excessively during the inflammatory reaction are transformed into fibrotic tissue, causing adhesion and fibrosis (32). Fibroblasts formed in surrounding tissues travel through the bloodstream to accumulate at the surgical site, resulting in fibrosis. The synthetic physical barrier prevents fibroblasts from sticking damaged tissues to surrounding tissues (33). Raftery *et al.* reported that chitosan reduced the formation of fibrotic tissue and inhibited the formation of collagen fibers (34). Chitosan also reduces fibrin deposition through hemostatic action and inhibits fibrosis formation by inhibiting transforming growth factor-beta (35). Moreover, chitosan inhibits cellular apoptosis by regulation of Sirtuin1 and reduces the inflammatory response (36). Gelatin induces epithelial and endothelial cell proliferation, but inhibits fibroblast proliferation (37). This study also confirmed that the anti-adhesion agent consisting of poloxamer, gelatin, and chitosan significantly reduced the incidence of adhesion and fibrosis after vasectomy. In addition, the number of inflammatory cells was remarkably small.

Anti-adhesion agent has been debated for its cost-effectiveness. If the preventive effect for PVPS is proven through the future clinical trials, the cost-effectiveness related to the use of anti-adhesion agents during vasectomy could be considered.

In this study, the experimental group showed more normal muscle layer structure than the control group, and the control group showed more deformation and damage than the normal tissue. The mechanism of PVPS could not be confirmed, but fibrosis and adhesion may have damaged the normal tissue structure and caused damage to the normal tissues due to many inflammatory reactions. Relatively a small sample size, short-term follow-up data, and the inability to evaluate the sterilization rate are the limitations of this study. Neural degeneration was not assessed. It would have been better to compare in both vas deferens of one animal, but it was unable because of the anatomical characteristics of the rat. Moreover, the present study could not confirm the exact mechanism of PVPS; however, the presence of significant fibrosis, adhesion, and inflammation after vasectomy were found in these cases. A pilot study in human will be needed to evaluate efficacy of anti-adhesion agent for prevent PVPS. Moreover, in the future, a randomized controlled trials are clearly needed to better elucidate the preventing effects against PVPS of anti-adhesion agent.

This study confirmed that the application of an anti-adhesion agent after vasectomy could suppress excessive inflammatory reactions and consequently prevent fibrosis and adhesion of tissues around the vas deferens, thereby reducing structural distortion. The prevention of adhesion, fibrosis, and inflammation may therefore reduce the occurrence of PVPS. Furthermore, the findings demonstrate the pre-clinical theoretical rationale for anti-adhesive effects at the vasectomy site for the prevention of PVPS.

Conclusions

In this study, the application of an anti-adhesion agent after vasectomy prevented the development of adhesion, fibrosis, and inflammation reaction and further reduced structural destruction. Although the mechanism of scrotal pain after vasectomy or PVPS has not been clearly elucidated,

adhesion and fibrosis have been suggested as one of the causes of PVPS. In this study, we proposed a possibility to reduce PVPS in humans through animal study, and further clinical studies are needed.

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Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-21-1170/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-21-1170/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-21-1170/coif). All authors report that the study was sponsored by CGBIO Co., Ltd. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Experiments were performed under a project license (No. EUIACUC 19-14) granted by Animal Experimental Ethics Committee of Eulji University, in compliance with institutional guidelines for the care and use of animals.

References

1. Yang F, Li J, Dong L, et al. Review of Vasectomy Complications and Safety Concerns. World J Mens Health 2021;39:406-18.
2. Tan WP, Levine LA. An overview of the management of post-vasectomy pain syndrome. Asian J Androl 2016;18:332-7.
3. Sinha V, Ramasamy R. Post-vasectomy pain syndrome: diagnosis, management and treatment options. Transl Androl Urol 2017;6:S44-7.
4. Whyte J, Sarrat R, Cisneros AI, et al. The vasectomized testis. Int Surg 2000;85:167-74.
5. Leslie TA, Illing RO, Cranston DW, et al. The incidence of chronic scrotal pain after vasectomy: a prospective audit. BJU Int 2007;100:1330-3.
6. Smith-Harrison LI, Smith RP. Vasectomy reversal for post-vasectomy pain syndrome. Transl Androl Urol 2017;6:S10-3.
7. Tandon S, Sabanegh E Jr. Chronic pain after vasectomy: a diagnostic and treatment dilemma. BJU Int 2008;102:166-9.
8. Linnet L, Hjort T. Sperm agglutinins in seminal plasma and serum after vasectomy: correlation between immunological and clinical findings. Clin Exp Immunol 1977;30:413-20.
9. Hattikudur NS, Shanta SR, Shahani SK, et al. Immunological and clinical consequences of vasectomy. Andrologia 1982;14:15-22.
10. Chung JH, Moon HS, Choi HY, et al. Inhibition of adhesion and fibrosis improves the outcome of epididymectomy as a treatment for chronic epididymitis: a multicenter, randomized controlled, single-blind study. J Urol 2013;189:1730-4.
11. Chung JH, Kim KS, Choi JD, et al. Effects of poloxamer-based thermo-sensitive sol-gel agent on urethral stricture after transurethral resection of the prostate for benign prostatic hyperplasia: a multicentre, single-blinded, randomised controlled trial. BJU Int 2020;125:160-7.
12. Park J, Kang H, Choi YS, et al. Prevention of Intra-Abdominal Adhesions Using the Combination of Mediclore® and a Statin. Eur Surg Res 2021. [Epub ahead of print]. doi: 10.1159/000519708.
13. Mazuji MK, Kalambaheti K, Pawar B. Prevention of adhesions with polyvinylpyrrolidone. preliminary report. Arch Surg 1964;89:1011-5.
14. Ozkan SB, Kir E, Culhaci N, et al. The effect of Seprafilm

on adhesions in strabismus surgery-an experimental study. J AAPOS 2004;8:46-9.
15. Sharlip ID, Belker AM, Honig S, et al. Vasectomy: AUA guideline. J Urol 2012;188:2482-91.
16. Auyeung AB, Almejally A, Alsaggar F, et al. Incidence of Post-Vasectomy Pain: Systematic Review and Meta-Analysis. Int J Environ Res Public Health 2020;17:1788.
17. Heidenreich A, Olbert P, Engelmann UH. Management of chronic testalgia by microsurgical testicular denervation. Eur Urol 2002;41:392-7.
18. Hori S, Sengupta A, Shukla CJ, et al. Long-term outcome of epididymectomy for the management of chronic epididymal pain. J Urol 2009;182:1407-12.
19. Lee JY, Cho KS, Lee SH, et al. A comparison of epididymectomy with vasectomy reversal for the surgical treatment of postvasectomy pain syndrome. Int Urol Nephrol 2014;46:531-7.
20. Black T, Francome C. Comparison of Marie Stopes scalpel and electrocautery no-scalpel vasectomy techniques. J Fam Plann Reprod Health Care 2003;29:32-4.
21. Cho SH, Min SK, Lee ST. Associations of ultrasonographic features with scrotal pain after vasectomy. Korean J Urol 2011;52:782-6.
22. Johnson D, Sandlow JI. Vasectomy: tips and tricks. Transl Androl Urol 2017;6:704-9.
23. Brochhausen C, Schmitt VH, Planck CN, et al. Current strategies and future perspectives for intraperitoneal adhesion prevention. J Gastrointest Surg 2012;16:1256-74.
24. diZerega GS, Campeau JD. Peritoneal repair and post-surgical adhesion formation. Hum Reprod Update 2001;7:547-55.
25. Cekinmez M, Erdogan B, Tufan K, et al. Is topical tissue plasminogen activator application effective on prevention of post-laminectomy epidural fibrosis? An experimental study. Neurol Res 2009;31:322-6.
26. Shin BS, Hu SK, Kim J, et al. Development of LC/MS/MS assay for the determination of 5-ethyl-2-{5-[4-(2-hydroxyethyl)piperazine-1-sulfonyl]-2-propoxyphenyl}-7-propyl- 3,5-dihydropyrrolo[3,2-d]pyrimidin-4-one (SK3530) in human plasma: application to a clinical pharmacokinetic study. J Pharm Biomed Anal 2007;45:176-84.
27. Kim TN, Chung MK, Nam JK, et al. Effectiveness of hyaluronic acid/carboxymethylcellulose in preventing adhesive bowel obstruction after laparoscopic radical cystectomy. Asian J Surg 2019;42:394-400.
28. Hu C, Tang F, Wu Q, et al. Novel Trilaminar Polymeric Antiadhesion Membrane Prevents Postoperative Pericardial Adhesion. Ann Thorac Surg 2021;111:184-9.
29. Oh SH, Kim JK, Song KS, et al. Prevention of postsurgical tissue adhesion by anti-inflammatory drug-loaded pluronic mixtures with sol-gel transition behavior. J Biomed Mater Res A 2005;72:306-16.
30. Dumortier G, Grossiord JL, Agnely F, et al. A review of poloxamer 407 pharmaceutical and pharmacological characteristics. Pharm Res 2006;23:2709-28.
31. Mi FL, Tan YC, Liang HF, et al. In vivo biocompatibility and degradability of a novel injectable-chitosan-based implant. Biomaterials 2002;23:181-91.
32. Fukui N, Fukuda A, Kojima K, et al. Suppression of fibrous adhesion by proteoglycan decorin. J Orthop Res 2001;19:456-62.
33. Li C, Wang H, Liu H, et al. The prevention effect of poly (L-glutamic acid)/chitosan on spinal epidural fibrosis and peridural adhesion in the post-laminectomy rabbit model. Eur Spine J 2014;23:2423-31.
34. Raftery RM, Woods B, Marques ALP, et al. Multifunctional biomaterials from the sea: Assessing the effects of chitosan incorporation into collagen scaffolds on mechanical and biological functionality. Acta Biomater 2016;43:160-9.
35. Wu W, Cheng R, das Neves J, et al. Advances in biomaterials for preventing tissue adhesion. J Control Release 2017;261:318-36.
36. Chen Q, Lu H, Yang H. Chitosan prevents adhesion during rabbit flexor tendon repair via the sirtuin 1 signaling pathway. Mol Med Rep 2015;12:4598-603.
37. Kim TI, Jung W, Chung JY, et al. Effect of a poloxamer-based thermosensitive gel on rotator cuff repair in a rabbit model: a controlled laboratory study. J Orthop Surg Res 2019;14:190.

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