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Effects of hyaluronic acid and carboxymethylcellulose on Urethral Stricture after Transurethral Resections of the Prostate for benign prostatic hyperplasia: A Multicentre, Single Blinded, Randomized Controlled Study

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Keyword:	Benign prostatic hyperplasia
Abstract:	Background: To evaluate the effect of hyaluronic acid (HA) and carboxymethylcellulose (CMC) instillation after transurethral resection of prostate (TURP) on preventing urethral stricture. Methods: A total of 180 patients who underwent TURP for BPH. Recruited patients were randomly divided into 2 groups: group A and B. Patients in group A (90 patients, experimental group) received HA/CMC instillation and patients in the group B (90 patients, control group) received lubricant instillation after TURP. Each patient was evaluated at 4 weeks (V1), 12 weeks (V2) and 24 weeks (V3) after the surgery. The effectiveness of HA/CMC instillation was evaluated based on the International Prostate Symptom Score (IPSS)/ Quality of Life (QoL), peak urine flow rate (Qmax), voided volume and post-voiding residual urine volume (PVR). The visual analogue scale (VAS) pain score and degree of satisfaction were also determined for each participant. Results: Among 180 initial participants, 80 patients in group A and 81 patients in group B had completed the experiment. VAS pain scores were 0.75 ± 0.75 and 1.75 ± 1.37 ($p<0.001$), and degrees of satisfaction were 0.63 ± 0.66 and 0.91 ± 0.51 in group A and group B at 1 month after surgery ($p=0.002$). By retrograde urethrography, urethral stricture after TURP was seen in 1 out of 80 subjects in group A and 7 out of 81 subjects in group B.

	Conclusions: HA/CMC instillation after TURP decreased the incidence of urethral stricture. In addition, HA/CMC was effective at reducing pain during the early post-operative period, with no adverse effects.

Reviewer: 1

Comments to the Author

It is very impressive that your nicely written manuscript is a a randomized prospective study with a control group, and it is an interesting finding that you discovered the use of hyaluronic acid and carboxymethylcellulose had such an impact on reducing the rate urethral stricture after TURP. However, your methods section is incomplete. For example, what dose/concentration of the medication (and control) was used. Exactly how was it administered? You said you placed an 18 gauge tube catheter between the urethral lumen and the Foley catheter. How long was the medication instilled? One time? continuously? Wat the catheter opening in the bladder or were there perforations along the tube allowing the medication to be in contact with the urethra.

Reply First of all, we would like to thank the reviewer for the positive and constructive comments. We have included one more figure in the revised manuscript, which explains the instillation of HA/CMC after TURP. Moreover, we have included more information regarding the instillation procedure in the figure legend. The high viscosity of HA/CMC means that its effect on the wound surface may be maintained for a long period of time. Also, chlorhexidine gel was used as the lubricant, which is the most common lubricant used for Foley catheterization.

- Thereafter, 5 mg of HA/CMC (Guardix-sol®; Hanmi Medicare, Seoul, Korea) or 5mg of lubricant (chlorhexidine gel) was instilled using an 18-gauge catheter inserted between the urethral lumen and the Foley catheter (Figure 1).

Moreover, the point of the paper is that this medication markedly reduces the risk of strictures after TURP using a 26 Fr sheaths and large catheters after surgery. However, you do not say where the strictures were located. Fossa? Bulbar? Length? I believe that more details are really needed. For example, strictures after instrumentation with large caliber catheters/scopes tend to involve the fossa navicularis. If the medication was instilled through a catheter into the bladder, I do not understand how this protects the fossa unless it is a systemic effect as the paper is missing this information.

Reply We pulled the Foley catheter in such a way that it blocked the bladder neck, which may help to retain the HA/CMC within the urethra. We have now commented on the site of urethral stricture in the

"Results" and "Discussion" section of the revised manuscript.

- The stricture site occurred in the bulbous urethra in one patient in group A, and in the bulbous urethra in three patients, the pendulous urethra in one patient, and the fossa navicularis in three patients in group B.
- However, the location of the urethral stricture site was not analyzed statistically in the present study due to the small number of patients affected. Moreover, no randomized studies have been performed to analyze the association between the urethral stricture site and the size of resectoscope.

Reviewer: 2

Comments to the Author

This is a generally well-done study, with potentially significant findings.

1) An overall comment is that the incidence of urethral stricture or bladder neck contracture is very low with 24 Fr instruments and bipolar energy. As the authors pointed out, the rate of stricture/contracture in their control group was high. This might limit the generalizability of their findings to patients in whom a 24 Fr instrument with bipolar energy is used.

Reply In accordance with the reviewer's comments, we have now addressed these limitations in the revised manuscript.

- Moreover the use of relatively large resectoscopic sheath may limit the generalizability of the findings reported in the present study.

2) In the conclusion of Abtract and in the beginning of the Discussion, it is stated that HA/CMC is effective for reducing pain after surgery. Please clarify that this was only at the early time point.

Reply We have corrected the manuscript according to the reviewer's suggestion.

<Abstract>

- In addition, HA/CMC was effective at reducing pain during the early post-operative period, with no adverse effects.

<Discussion>

- In addition, it improved the post-surgical outcomes by helping to reduce pain during the early post-operative period, thereby increasing patient satisfaction levels.

3) Why was the study "open-label?" At the very least the patients could have been blinded. Are there characteristics of HA/CMC that make it obvious to the patient?

Reply Thank you for pointing this out. We apologize for not making this clear. The study has conducted in a single-blinded manner. We have now revised the “Materials and Methods” section as follows

- This was a randomized, single blinded, multi-centre, prospective study undertaken by 10 surgeons at seven participating medical institutions.

4) It is indicated that each of 10 surgeons did 9 experimental and 9 control patients. Confirm that the randomization therefore was "block randomization", meaning that there were 10 randomization tables, one for each surgeon.

Reply We have now corrected the manuscript as per the reviewer’s suggestion.

- A simple block randomization method was used to assign patients to either (1) an experimental group (90 patients; group A), which received HA/CMC instillation after TURP, or (2) a control group (90 patients; group B), which received lubricant instillation after TURP.

5) Was power calculation done, and if so what were the parameters?

Reply This was a pilot study. Therefore, we did not perform a power calculation. This has now been mentioned as a study limitation in the revised manuscript

- We did not perform a power calculation.

6) The authors should compare the demographics between those lost to follow-up to those completing the study, which helps provide an assessment of the potential bias introduced by the loss of those patients.

Reply Thank you for pointing this out. There was no statistically significant difference in the baseline

characteristics and perioperative outcomes between the patients lost to follow-up and those completing the study. We have now included this statement in the “Results” section of the revised manuscript

- There was no statistically significant difference in the baseline characteristics and perioperative outcomes between the patients lost to follow-up and those completing the study.

7) Please include the p-values in the text, and not just the table, provided that word-count allows.

Reply As requested, we have now included p-values in the text.

- One patient in group A experienced intra-operative capsule perforation and one patient in group B required an intra-operative transfusion (p=0.316). Three patients in group A and two patients in group B experienced post-operative clot retention (p=0.642), while two patients in group A required a post-operative transfusion (p=0.154). One patient in group B experienced the onset of epididymo-orchitis (p=0.322). Nine patients (11.25%) in group A and 19 (23.46%) in group B experienced a urethral stricture according to uroflowmetry (p=0.041). According to retrograde urethrography, one patient in group A and seven patients in group B had a confirmed urethral stricture (p=0.031) (Table 2).

8) I think that the last word of the last sentence of the first complete paragraph on page 11 should be "Internal urethrotomy" not "TURP."

Reply Thank you. We have replaced “TURP” with "internal urethrotomy".

- In this study, HA/CMC was used to reduce the incurrence of post-TURP urethral stricture based on the results of previous studies about the usefulness and scar formation inhibition properities of HA/CMC as solution synthetic physical barrier for internal urethrotomy.[27]

9) The lines in the 6 first figures are too small; make the lines thicker, and use a scheme that will allow more clear distinction between the 2 groups

Reply We initially made the required corrections to Figure 3. Despite this, however, the distinction between the two groups was still not clear. Therefore, we have used a different style of graph.

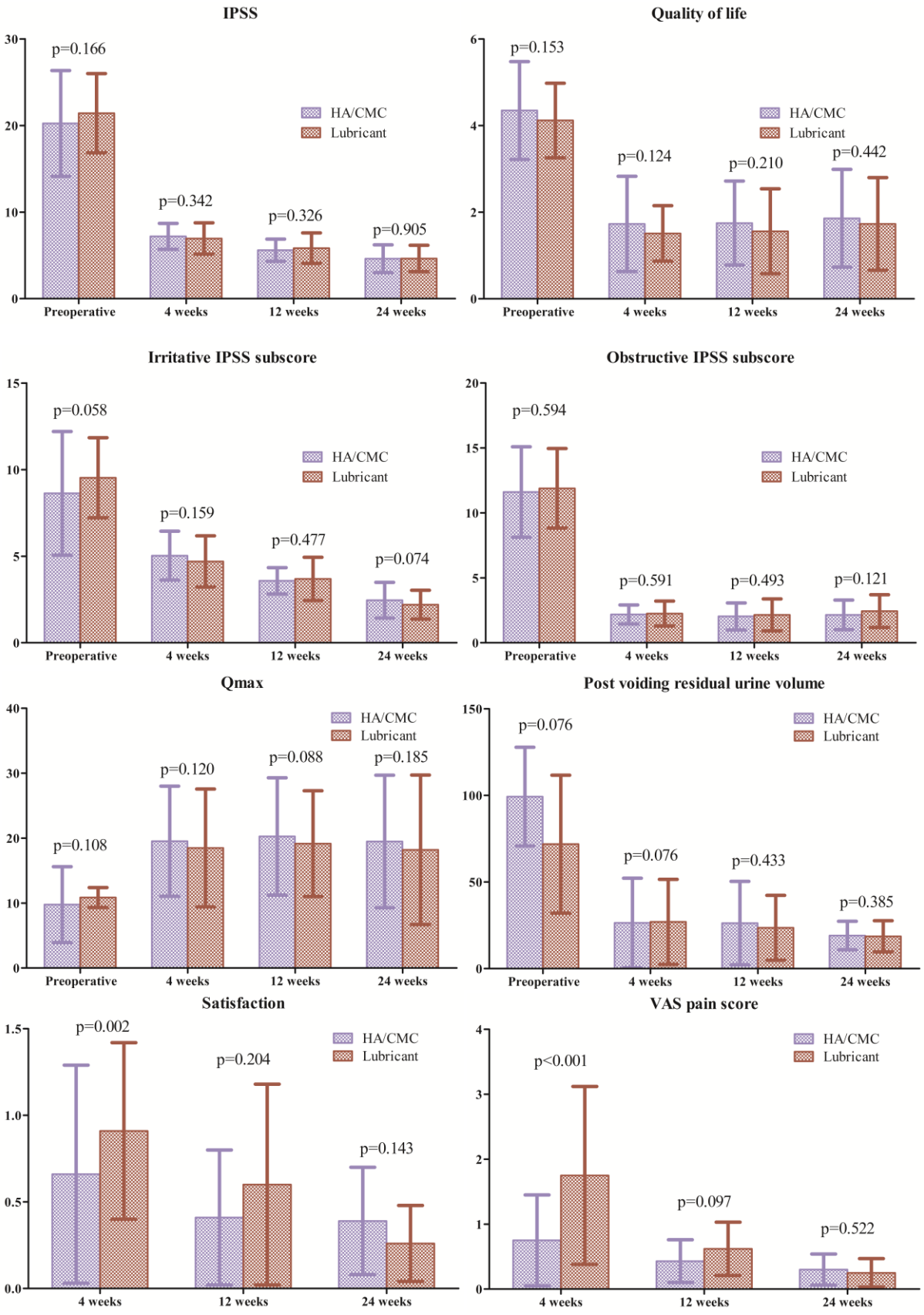
Figure 1.

A: HA/CMC (5 mg) was instilled after TURP via an 18-gauze tube catheter.

B: After ballooning (to a volume of 30 cc) the urethral Foley catheter was pulled back to block the bladder neck. HA/CMC was then instilled between the urethral lumen and the Foley catheter.

C: A gauze was used to maintain traction for 1 day after surgery to retain the HA/CMC within the urethra.

Figure 2


IPSS
p=0.166
p=0.342
p=0.326
p=0.905
HA/CMC
Lubricant
Preoperative
4 weeks
12 weeks
24 weeks
Quality of life
p=0.153
p=0.124
p=0.210
p=0.442
Irritative IPSS subscore
p=0.058
p=0.159
p=0.477
p=0.074
Obstructive IPSS subscore
p=0.594
p=0.591
p=0.493
p=0.121
Qmax
p=0.108
p=0.120
p=0.088
p=0.185
Post voiding residual urine volume
p=0.076
p=0.076
p=0.433
p=0.385
Satisfaction
p=0.002
p=0.204
p=0.143
VAS pain score
p<0.001
p=0.097
p=0.522

Abbreviations

HA = Hyaluronic acid

CMC = Carboxymethylcellulose

TURP = Transurethral resection of prostate

BPH = Benign prostatic hyperplasia

IPSS = International prostate symptom score

QoL = Quality of life

VAS = Visual analogue scale

Qmax = Peak urine flow rate

PVR = Post-voiding residual urine volume

LUTS = Lower urinary tract symptoms

Effects of hyaluronic acid and carboxymethylcellulose on Urethral Stricture after Transurethral Resections of the Prostate for benign prostatic hyperplasia: A Multicentre, Single Blinded, Randomized Controlled Study,

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Abstract

Background: To evaluate the effect of hyaluronic acid (HA) and carboxymethylcellulose (CMC) instillation after transurethral resection of prostate (TURP) on preventing urethral stricture.

Methods: A total of 180 patients who underwent TURP for BPH. Recruited patients were randomly divided into 2 groups: group A and B. Patients in group A (90 patients, experimental group) received HA/CMC instillation and patients in the group B (90 patients, control group) received lubricant instillation after TURP. Each patient was evaluated at 4 weeks (V1), 12 weeks (V2) and 24 weeks (V3) after the surgery. The effectiveness of HA/CMC instillation was evaluated based on the International Prostate Symptom Score (IPSS)/ Quality of Life (QoL), peak urine flow rate (Qmax), voided volume and post-voiding residual urine volume (PVR). The visual analogue scale (VAS) pain score and degree of satisfaction were also determined for each participant.

Results: Among 180 initial participants, 80 patients in group A and 81 patients in group B had completed the experiment. VAS pain scores were 0.75 ± 0.75 and 1.75 ± 1.37 ($p<0.001$), and degrees of satisfaction were 0.63 ± 0.66 and 0.91 ± 0.51 in group A and group B at 1 month after surgery ($p=0.002$). By retrograde urethrography, urethral stricture after TURP was seen in 1 out of 80 subjects in group A and 7 out of 81 subjects in group B.

Conclusions: HA/CMC instillation after TURP decreased the incidence of urethral stricture. In addition, HA/CMC was effective at reducing pain during the early post-operative period, with no adverse effects.

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Introduction

Benign prostatic hyperplasia (BPH) causes lower urinary tract symptoms (LUTS) and is one of the most common diseases of aging male.[1] BPH is histologically observed in almost half of men in their 60s and in most men in their 80s.[2] BPH leading to LUTS reduces quality of life by disturbing normal activities and sleeping, and causing complications such as urinary tract infection or acute urinary retention. Currently, several types of medications are available to treat LUTS accompanying BPH (LUTS/BPH) such as alpha adrenergic blockers, 5-alpha-reductase inhibitors and others. In addition, surgical treatment methods have been introduced including resection or enucleation. Currently the most popular and effective treatment for LUTS/BPH is transurethral resection of the prostate (TURP).[3-4] However, TURP is associated with postoperative complications such as bleeding, a prolonged in-patient period, pain and infection as well as late complications including urethral stricture, incontinence, erectile dysfunction, retrograde ejaculation and bladder neck contraction.[5] Other methods have been studied to reduce incurrence of post-TURP urethral stricture by performing TURP with small diameter resectoscopes or warm saline.[6-7]

Recently, synthetic physical barriers have been developed to supplement cases in which the natural barrier has been damaged. Of these representative substances are hyaluronic acid (HA) and carboxymethylcellulose (CMC). HA is an anionic polysaccharide demonstrating high levels of Polymerization, hydrophilicity and non-immunity as well as viscoelastic properties. As the active ingredient of the extracellular matrix, it coats the mucosal surface and provides lubricating action. From such actions of coating mucosal surface, possibility of trauma

reduction on the surgery site is being recommended.[8] CMC is also an anionic polysaccharide, which is an inducer of more hydrophilically modified cellulose with the glucosidic hydroxyl group had been carboxymethylationized and has been used as an excipient, viscosifier, lubricans and stabilizer for pharmaceutical products, cosmetics and food.[9] HA and CMC (HA/CMC) has been used in surgical procedures for preventing the postoperative adhesion.[10] However, no study has examined the preventive effects of using HA/CMC for TURP of the urethral stricture. To this end, this study aimed to identify the effectiveness of HA/CMC in preventing urethral stricture formation after TURP for treatment of LUTS/BPH.

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Patients and methods

Subjects and study design

For this study, 180 patients with LUTS/BPH who received TURP from June, 2010 to May, 2011 were recruited. This was a randomized, single blinded, multi-centre, prospective study undertaken by 10 surgeons at seven participating medical institutions. Each surgeons performed equal number of TURP (experiment:9, control:9). The study was implemented after obtaining the approval of the institutional review board.

Included subjects (1) underwent TURP after clinical diagnosis with BPH, and (2) were willing and able to participate. Excluded from the study were patients with diagnoses of (1) prostatic hypertrophy treated with endoscopic or invasive procedures of prostatetomy, (2) urethral stricture, which is diagnosed by cystoscope, (3) neurogenic bladder, or (4) a urinary tract infection.

A simple block randomization method was used to assign patients to either (1) an experimental group (90 patients; group A), which received HA/CMC instillation after TURP, or (2) a control group (90 patients; group B), which received lubricant instillation after TURP.

The primary endpoint is the occurrence rates of urethral stricture and secondary endpoints are voiding symptoms, satisfaction and degree of pain were evaluated.

Before enrollment (V0), information regarding illness duration and past medical history was collected. Routine hematological tests and urinalysis were performed. Patients were assessed during visits at postoperative week 4 (V1), week 12 (V2) and week 24 (V3).

Surgical Technique

TURP was performed in the following sequence of directions: 6 o'clock, 3 o'clock, 12 o'clock and 9 o'clock. We used a #26 Fr. resectoscopic sheath, 30° telescope and bipolar resector. By inserting a 3way, 30cc balloon, #22 Fr. urethral Foley catheter and enveloped and binding the tip of urethra. Thereafter, 5 mg of HA/CM (Guardix-sol®; Hanmi Medicare, Seoul, Korea) or 5mg of lubricant (chlorhexidine gel) was instilled using an 18-gauge catheter inserted between the urethral lumen and the Foley catheter (Figure 1). Post-instillation traction was retained for 1 day before removal. While keeping the traction of the Foley catheter, the patients kept on bed rest.

Assessment of efficacy and safety

Efficacy of HA/CMC was assessed to prevent urethral stricture at each postoperative visit by determining the International Prostate Symptom Score (IPSS) and by measuring the peak urine flow rate (Qmax), and the post-voiding residual urine volume (PVR). The quality of life (QoL) score was also determined. During the postoperative in-patient period, assessments were made of the indwelling time of the Foley catheter, degree of pain, and level of satisfaction. Constrictive uroflow curves or a maximum flow rate ≤ 10 mL/s by uroflowmetry was considered to indicate the occurrence of a urethral stricture. To distinguish urethral stricture from bladder neck contracture, urethral stricture was confirmed by urethroscopy and urethrography. Assessment of pain and satisfaction level were conducted with the 0 to 10 point Likert scale visual analogue scale (VAS) pain score and a 0 point (very satisfied) to 3 point (very unsatisfied) Likert scale. The safety of HA/CMC treatment was assessed at V1, V2, and V3 by taking patient history, performing a physical examination and recording adverse

effects..

Statistical analysis

The occurrence of urethral stricture rate was evaluated by per protocol analysis based on the number of patients who completed the study. Preoperative characteristics, including prostate volume, and perioperative outcomes were evaluated by intent-to-treat analysis. Voiding symptoms, Qmax and PVR were compared by using Student's paired *t*-test. The patients who had no occurrence of urethral stricture were compared to those who had occurrence in terms of voiding symptoms, pain scale, and degree of satisfaction. SPSS software v.18.0 was used for statistical analysis, and a p value <0.05 was considered to be statistically significant.

Results

Of 180 total patients, 10 in group A and 9 in group B were lost to follow-up and were excluded. Analyses were performed using data collected from the records of 80 patients in group A and 81 patients in group B, who fulfilled the follow-up period (Figure 2). There was no statistically significant difference in the baseline characteristics and perioperative outcomes between the patients lost to follow-up and those completing the study. One patient in group A experienced intra-operative capsule perforation and one patient in group B required an intra-operative transfusion (p=0.316). Three patients in group A and two patients in group B experienced post-operative clot retention (p=0.642), while two patients in group A required a post-operative transfusion (p=0.154). One patient in group B experienced the onset of epididymo-orchitis (p=0.322). Nine patients (11.25%) in group A and 19 (23.46%) in group B experienced a urethral stricture according to uroflowmetry (p=0.041). According to retrograde urethrography, one patient in group A and seven patients in group B had a confirmed urethral stricture (p=0.031) (Table 2). The stricture site occurred in the bulbous urethra in one patient in group A, and in the bulbous urethra in three patients, the pendulous urethra in one patient, and the fossa navicularis in three patients in group B.

Preoperative characteristics were well balanced between the groups. Resected prostate volumes, indwelling days of Foley catheter and LOS had no significant difference between both groups (Table 1).

At each visit after surgery, the patients showed no significant difference of voiding symptoms between groups At week 4 (V1) postoperative, the satisfaction levels were 0.63±0.66 for group A and 0.91±0.51 for group B (p=0.002), while VAS pain scales were 0.75±0.75 for group A and 1.75±1.37for group B (p<0.001) (Figure 3).

Discussion

This study aimed to assess the effects of HA/CMC instillation into the urethra during TURP at the onset of urethral stricture. We found that HA/CMC was effective for prevention of urethral stricture with no specific side effects. In addition, it improved the post-surgical outcomes by helping to reduce pain during the early post-operative period, thereby increasing patient satisfaction levels.

BPH incurs by histological proliferation of smooth muscle and epithelial cells in the prostatic transitional zone.[11] The objective in LUTS/BPH treatment is to improve the quality of life and to treat and prevent complications including urinary tract obstruction, urinary retention, and infection. Therapeutic methods are largely divided into watchful waiting, medical management and surgical management.[12] Of these, watchful waiting is applicable to patients with mild symptoms or with moderate-to-severe symptoms but no complications. This treatment requires annual measurement of prostate volume as well as assessment of flow rate.[13] For medical management, representative drugs are alpha adrenergic blockers and 5 alpha-reductase inhibitors (5ARI). 5ARI lowers serum dihydrotestosterone and reduces prostate volume to relieve symptoms.[14] Alpha adrenergic blockers do not affect prostate volume or prostate specific antigen values, but improve symptoms through the relaxation of smooth muscle cells in the prostate.[15] However, when patients show moderate-to-severe symptoms accompanied by complications such as infection, hematuria or upper urinary tract obstruction, or when they do not improve with medical management, indications suggest surgical management. Moreover, surgical management is increasingly being offered for control of lower urinary tract symptoms.[16] Surgical management technique include open prostatectomy, transurethral vaporization, transurethral resection

of the prostate (TURP), transurethral holmium laser ablation/enucleation, holmium laser resection, photoselective vaporization and transurethral incision, but TURP is still the gold standard for surgical treatment of LUTS/BPH.[13] TURP resects the prostate using radiofrequency energy. Despite advancements in surgical techniques and instruments, TURP faces many challenges such as morbidity, a long in-patient time and long indwelling time of the Foley catheter; also infection, bleeding, incontinence, reterograde ejaculation and urethral stricture.[17] Urethral stricture after TURP is a considerable complication with an incidence rate of 1.2-29%.[5, 18-19] Large variation in the prevalence of urethral stricture is seen because of the absence of clear descriptive criteria for urethral stricture. According to Desmond et al., peak urine flow reduced to ≤ 10mL/s is the diagnosis for urethral stricture.[20] In present study, urethral stricture was defined as constrictive uroflow curves or a maximum flow rate ≤ 10mL/s by uroflowmetry and when the stricture site was observable by urethroscopy or urethrogram. Occurrence rate of urethral stricture was 8.64% in present study, this relatively high number of occurrence may related that we used only #26 Fr. resectoscopic sheath, which is relatively larger size, even though there has no resistance of resectoscope passage. However, the location of the urethral stricture site was not analyzed statistically in the present study due to the small number of patients affected. Moreover, no randomized studies have been performed to analyze the association between the urethral stricture site and the size of resectoscope.

Other studies Urethral stricture often occurs after TURP and the triggering factors reported include infection, mechanical injury and indwelling of the Foley catheter.[21] During TURP, the instrument moves into the urethra a mean of 800 times, causing mechanical injury. In addition, indwelling of the Foley catheter causes ischemia of the urethra, or the catheter itself might cause mechanical injury.[22] During tissue development, remodeling and wound healing of the mechanical injury site, urethral stricture is caused by scar formation and fibrosis. In these

cases, extracellular matrix regulation plays a prominent role in this process, which sodium hyaluronate may inhibit to reduce unwanted scar tissue by50% or more.[23] In addition, animal studies by Hong et al., reported that fewer fibrous tissues were observed by histological test on a group postoperatively coated with HA/CMC.[10]

Several natural barriers including the peritoneum, omentum, and amnion prevent adhesion between tissues.[24] However, when this barrier is damaged after surgery, synthetic physical barriers are needed to separate the injured tissue surface from the surrounding organs.[25] These include film barriers, solution barriers, and recently developed sol-gel transition barriers.[26] Among these, solution barriers and sol-gel transition barriers can be used for post-TURP instillation between the urethra, bladder neck and Foley catheter. HA/CMC is a liquid type synthetic physical sol-gel barrier with viscosity from 2500 to 3500 cP.[10] In this study, HA/CMC was used to reduce the incurrence of post-TURP urethral stricture based on the results of previous studies about the usefulness and scar formation inhibition properities of HA/CMC as solution synthetic physical barrier for internal urethrotomy.[27]

No differences were seen in the test group treated with HA/CMC and the control group for IPSS, QoL or uroflowmetry among patients in whom no urethral stricture had occurred. Thus HA/CMC did not appear to affect postoperative voiding symptoms. However, significant differences were seen in the postoperative pain scale and occurrence rate of urethral stricture. HA/CMC is a solution synthetic physical barrier with high viscosity that is expected to be effective, since it maintains a long contact time when coated onto a tissue surface. HA/CMC instillation during TURP might reduce the postoperative occurrence of urethral stricture because of its efficacy to prevent fibrosis and scar formation during the healing of the stricture resected site and mechanical

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injury inside the urethra. Moreover, reducing pain of experimental group may come from longer sustain of lubrication between the prostatectomy site, urethra injury site and Foley catheter than control group.

Limitations of this study were the relatively short follow-up and absence of animal study. We did not perform a power calculation Moreover the use of relatively large resectoscopic sheath may limit the generalizability of the findings reported in the present study. However, this is the first prospective, randomized controlled study to identify the usefulness of HA/CMC for reducing the incidence of post-TURP urethral stricture formation. Whether the efficacy of HA/CMC can be maintained persistently through long-term follow-up observations must be determined, and identification of the histological actions of the post-TURP use of HA/CMC requires animal studies.

Conclusion

The results of our study indicate that use of HA/CMC in the urethra during TURP decreases the incidence of urethral stricture. It showed effectiveness in reducing postoperative pain with no side effects, and improved patient satisfaction.

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Disclosures

Dr. Jae Hoon Chung, Dr. Dong Hyuk Kang, Dr. Hong Sang Moon, Dr. Tae Yung Jeong, Dr. U-Syn Ha, Dr. June Hyun Han, Dr. Ji Hyeong Yu, Dr. Jeong Man Cho, Dr. Tag Keun Yoo, Dr. Jinsung Park, Dr. Tae Hyo Kim and Dr. Seung Wook Lee have no conflict of interest or financial ties to disclose.

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Figure legend

Figure 1. Instillation of HA/CMC on urethra using 18-gauze catheter

A: HA/CMC (5 mg) was instilled after TURP via an 18-gauze tube catheter.

B: After ballooning (to a volume of 30 cc) the urethral Foley catheter was pulled back to block the bladder neck. HA/CMC was then instilled between the urethral lumen and the Foley catheter.

C: A gauze was used to maintain traction for 1 day after surgery to retain the HA/CMC within the urethra.

Figure 2. The 26 weeks study with 2 weeks screening period and 24 weeks treatment phase

Figure 3. Surgical outcomes of the experimental group and the control group after TURP at each follow-up time point

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Effects of hyaluronic acid and carboxymethylcellulose on Urethral Stricture after Transurethral Resections of the Prostate for benign prostatic hyperplasia: A Multicentre, Single Blinded, Randomized Controlled Study

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Abstract

Background: To evaluate the effect of hyaluronic acid (HA) and carboxymethylcellulose (CMC) instillation after transurethral resection of prostate (TURP) on preventing urethral stricture.

Methods: A total of 180 patients who underwent TURP for BPH. Recruited patients were randomly divided into 2 groups: group A and B. Patients in group A (90 patients, experimental group) received HA/CMC instillation and patients in the group B (90 patients, control group) received lubricant instillation after TURP. Each patient was evaluated at 4 weeks (V1), 12 weeks (V2) and 24 weeks (V3) after the surgery. The effectiveness of HA/CMC instillation was evaluated based on the International Prostate Symptom Score (IPSS)/ Quality of Life (QoL), peak urine flow rate (Qmax), voided volume and post-voiding residual urine volume (PVR). The visual analogue scale (VAS) pain score and degree of satisfaction were also determined for each participant.

Results: Among 180 initial participants, 80 patients in group A and 81 patients in group B had completed the experiment. VAS pain scores were 0.75 ± 0.75 and 1.75 ± 1.37 ($p<0.001$), and degrees of satisfaction were 0.63 ± 0.66 and 0.91 ± 0.51 in group A and group B at 1 month after surgery ($p=0.002$). By retrograde urethrography, urethral stricture after TURP was seen in 1 out of 80 subjects in group A and 7 out of 81 subjects in group B.

Conclusions: HA/CMC instillation after TURP decreased the incidence of urethral stricture. In addition, HA/CMC was effective at reducing pain during the early post-operative period, with no adverse effects.

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Introduction

Benign prostatic hyperplasia (BPH) causes lower urinary tract symptoms (LUTS) and is one of the most common diseases of aging male.[1] BPH is histologically observed in almost half of men in their 60s and in most men in their 80s.[2] BPH leading to LUTS reduces quality of life by disturbing normal activities and sleeping, and causing complications such as urinary tract infection or acute urinary retention. Currently, several types of medications are available to treat LUTS accompanying BPH (LUTS/BPH) such as alpha adrenergic blockers, 5-alpha-reductase inhibitors and others. In addition, surgical treatment methods have been introduced including resection or enucleation. Currently the most popular and effective treatment for LUTS/BPH is transurethral resection of the prostate (TURP).[3-4] However, TURP is associated with postoperative complications such as bleeding, a prolonged in-patient period, pain and infection as well as late complications including urethral stricture, incontinence, erectile dysfunction, retrograde ejaculation and bladder neck contraction.[5] Other methods have been studied to reduce incurrence of post-TURP urethral stricture by performing TURP with small diameter resectoscopes or warm saline.[6-7]

Recently, synthetic physical barriers have been developed to supplement cases in which the natural barrier has been damaged. Of these representative substances are hyaluronic acid (HA) and carboxymethylcellulose (CMC). HA is an anionic polysaccharide demonstrating high levels of Polymerization, hydrophilicity and non-immunity as well as viscoelastic properties. As the active ingredient of the extracellular matrix, it coats the mucosal surface and provides lubricating action. From such actions of coating mucosal surface, possibility of trauma

reduction on the surgery site is being recommended.[8] CMC is also an anionic polysaccharide, which is an inducer of more hydrophilically modified cellulose with the glucosidic hydroxyl group had been carboxymethylationized and has been used as an excipient, viscosifier, lubricans and stabilizer for pharmaceutical products, cosmetics and food.[9] HA and CMC (HA/CMC) has been used in surgical procedures for preventing the postoperative adhesion.[10] However, no study has examined the preventive effects of using HA/CMC for TURP of the urethral stricture. To this end, this study aimed to identify the effectiveness of HA/CMC in preventing urethral stricture formation after TURP for treatment of LUTS/BPH.

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Patients and methods

Subjects and study design

For this study, 180 patients with LUTS/BPH who received TURP from June, 2010 to May, 2011 were recruited. This was a randomized, single blinded, multi-centre, prospective study undertaken by 10 surgeons at seven participating medical institutions. Each surgeons performed equal number of TURP (experiment:9, control:9). The study was implemented after obtaining the approval of the institutional review board.

Included subjects (1) underwent TURP after clinical diagnosis with BPH, and (2) were willing and able to participate. Excluded from the study were patients with diagnoses of (1) prostatic hypertrophy treated with endoscopic or invasive procedures of prostatetomy, (2) urethral stricture, which is diagnosed by cystoscope, (3) neurogenic bladder, or (4) a urinary tract infection.

A simple block randomization method was used to assign patients to either (1) an experimental group (90 patients; group A), which received HA/CMC instillation after TURP, or (2) a control group (90 patients; group B), which received lubricant instillation after TURP.

The primary endpoint is the occurrence rates of urethral stricture and secondary endpoints are voiding symptoms, satisfaction and degree of pain were evaluated.

Before enrollment (V0), information regarding illness duration and past medical history was collected. Routine hematological tests and urinalysis were performed. Patients were assessed during visits at postoperative week 4 (V1), week 12 (V2) and week 24 (V3).

Surgical Technique

TURP was performed in the following sequence of directions: 6 o'clock, 3 o'clock, 12 o'clock and 9 o'clock. We used a #26 Fr. resectoscopic sheath, 30° telescope and bipolar resector. By inserting a 3way, 30cc balloon, #22 Fr. urethral Foley catheter and enveloped and binding the tip of urethra. Thereafter, 5 mg of HA/CMC (Guardix-sol®; Hanmi Medicare, Seoul, Korea) or 5mg of lubricant (chlorhexidine gel) was instilled using an 18-gauge catheter inserted between the urethral lumen and the Foley catheter (Figure 1). Post-instillation traction was retained for 1 day before removal. While keeping the traction of the Foley catheter, the patients kept on bed rest.

Assessment of efficacy and safety

Efficacy of HA/CMC was assessed to prevent urethral stricture at each postoperative visit by determining the International Prostate Symptom Score (IPSS) and by measuring the peak urine flow rate (Qmax), and the post-voiding residual urine volume (PVR). The quality of life (QoL) score was also determined. During the postoperative in-patient period, assessments were made of the indwelling time of the Foley catheter, degree of pain, and level of satisfaction. Constrictive uroflow curves or a maximum flow rate ≤ 10 mL/s by uroflowmetry was considered to indicate the occurrence of a urethral stricture. To distinguish urethral stricture from bladder neck contracture, urethral stricture was confirmed by urethroscopy and urethrography. Assessment of pain and satisfaction level were conducted with the 0 to 10 point Likert scale visual analogue scale (VAS) pain score and a 0 point (very satisfied) to 3 point (very unsatisfied) Likert scale. The safety of HA/CMC treatment was assessed at V1, V2, and V3 by taking patient history, performing a physical examination and recording adverse

effects..

Statistical analysis

The occurrence of urethral stricture rate was evaluated by per protocol analysis based on the number of patients who completed the study. Preoperative characteristics, including prostate volume, and perioperative outcomes were evaluated by intent-to-treat analysis. Voiding symptoms, Qmax and PVR were compared by using Student's paired *t*-test. The patients who had no occurrence of urethral stricture were compared to those who had occurrence in terms of voiding symptoms, pain scale, and degree of satisfaction. SPSS software v.18.0 was used for statistical analysis, and a p value <0.05 was considered to be statistically significant.

Results

Of 180 total patients, 10 in group A and 9 in group B were lost to follow-up and were excluded. Analyses were performed using data collected from the records of 80 patients in group A and 81 patients in group B, who fulfilled the follow-up period (Figure 2). There was no statistically significant difference in the baseline characteristics and perioperative outcomes between the patients lost to follow-up and those completing the study. One patient in group A experienced intra-operative capsule perforation and one patient in group B required an intra-operative transfusion (p=0.316). Three patients in group A and two patients in group B experienced post-operative clot retention (p=0.642), while two patients in group A required a post-operative transfusion (p=0.154). One patient in group B experienced the onset of epididymo-orchitis (p=0.322). Nine patients (11.25%) in group A and 19 (23.46%) in group B experienced a urethral stricture according to uroflowmetry (p=0.041). According to retrograde urethrography, one patient in group A and seven patients in group B had a confirmed urethral stricture (p=0.031) (Table 2). The stricture site occurred in the bulbous urethra in one patient in group A, and in the bulbous urethra in three patients, the pendulous urethra in one patient, and the fossa navicularis in three patients in group B.

Preoperative characteristics were well balanced between the groups. Resected prostate volumes, indwelling days of Foley catheter and LOS had no significant difference between both groups (Table 1).

At each visit after surgery, the patients showed no significant difference of voiding symptoms between groups At week 4 (V1) postoperative, the satisfaction levels were 0.63±0.66 for group A and 0.91±0.51 for group B (p=0.002), while VAS pain scales were 0.75±0.75 for group A and 1.75±1.37for group B (p<0.001) (Figure 3).

Discussion

This study aimed to assess the effects of HA/CMC instillation into the urethra during TURP at the onset of urethral stricture. We found that HA/CMC was effective for prevention of urethral stricture with no specific side effects. In addition, it improved the post-surgical outcomes by helping to reduce pain during the early post-operative period, thereby increasing patient satisfaction levels.

BPH incurs by histological proliferation of smooth muscle and epithelial cells in the prostatic transitional zone.[11] The objective in LUTS/BPH treatment is to improve the quality of life and to treat and prevent complications including urinary tract obstruction, urinary retention, and infection. Therapeutic methods are largely divided into watchful waiting, medical management and surgical management.[12] Of these, watchful waiting is applicable to patients with mild symptoms or with moderate-to-severe symptoms but no complications. This treatment requires annual measurement of prostate volume as well as assessment of flow rate.[13] For medical management, representative drugs are alpha adrenergic blockers and 5 alpha-reductase inhibitors (5ARI). 5ARI lowers serum dihydrotestosterone and reduces prostate volume to relieve symptoms.[14] Alpha adrenergic blockers do not affect prostate volume or prostate specific antigen values, but improve symptoms through the relaxation of smooth muscle cells in the prostate.[15] However, when patients show moderate-to-severe symptoms accompanied by complications such as infection, hematuria or upper urinary tract obstruction, or when they do not improve with medical management, indications suggest surgical management. Moreover, surgical management is increasingly being offered for control of lower urinary tract symptoms.[16] Surgical management technique include open prostatectomy, transurethral vaporization, transurethral resection

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of the prostate (TURP), transurethral holmium laser ablation/enucleation, holmium laser resection, photoselective vaporization and transurethral incision, but TURP is still the gold standard for surgical treatment of LUTS/BPH.[13] TURP resects the prostate using radiofrequency energy. Despite advancements in surgical techniques and instruments, TURP faces many challenges such as morbidity, a long in-patient time and long indwelling time of the Foley catheter; also infection, bleeding, incontinence, reterograde ejaculation and urethral stricture.[17] Urethral stricture after TURP is a considerable complication with an incidence rate of 1.2-29%.[5, 18-19] Large variation in the prevalence of urethral stricture is seen because of the absence of clear descriptive criteria for urethral stricture. According to Desmond et al., peak urine flow reduced to ≤ 10mL/s is the diagnosis for urethral stricture.[20] In present study, urethral stricture was defined as constrictive uroflow curves or a maximum flow rate ≤ 10mL/s by uroflowmetry and when the stricture site was observable by urethroscopy or urethrogram. Occurrence rate of urethral stricture was 8.64% in present study, this relatively high number of occurrence may related that we used only #26 Fr. resectoscopic sheath, which is relatively larger size, even though there has no resistance of resectoscope passage. However, the location of the urethral stricture site was not analyzed statistically in the present study due to the small number of patients affected. Moreover, no randomized studies have been performed to analyze the association between the urethral stricture site and the size of resectoscope.

Other studies Urethral stricture often occurs after TURP and the triggering factors reported include infection, mechanical injury and indwelling of the Foley catheter.[21] During TURP, the instrument moves into the urethra a mean of 800 times, causing mechanical injury. In addition, indwelling of the Foley catheter causes ischemia of the urethra, or the catheter itself might cause mechanical injury.[22] During tissue development, remodeling and wound healing of the mechanical injury site, urethral stricture is caused by scar formation and fibrosis. In these

cases, extracellular matrix regulation plays a prominent role in this process, which sodium hyaluronate may inhibit to reduce unwanted scar tissue by50% or more.[23] In addition, animal studies by Hong et al., reported that fewer fibrous tissues were observed by histological test on a group postoperatively coated with HA/CMC.[10]

Several natural barriers including the peritoneum, omentum, and amnion prevent adhesion between tissues.[24] However, when this barrier is damaged after surgery, synthetic physical barriers are needed to separate the injured tissue surface from the surrounding organs.[25] These include film barriers, solution barriers, and recently developed sol-gel transition barriers.[26] Among these, solution barriers and sol-gel transition barriers can be used for post-TURP instillation between the urethra, bladder neck and Foley catheter. HA/CMC is a liquid type synthetic physical sol-gel barrier with viscosity from 2500 to 3500 cP.[10] In this study, HA/CMC was used to reduce the incurrence of post-TURP urethral stricture based on the results of previous studies about the usefulness and scar formation inhibition properities of HA/CMC as solution synthetic physical barrier for internal urethrotomy.[27]

No differences were seen in the test group treated with HA/CMC and the control group for IPSS, QoL or uroflowmetry among patients in whom no urethral stricture had occurred. Thus HA/CMC did not appear to affect postoperative voiding symptoms. However, significant differences were seen in the postoperative pain scale and occurrence rate of urethral stricture. HA/CMC is a solution synthetic physical barrier with high viscosity that is expected to be effective, since it maintains a long contact time when coated onto a tissue surface. HA/CMC instillation during TURP might reduce the postoperative occurrence of urethral stricture because of its efficacy to prevent fibrosis and scar formation during the healing of the stricture resected site and mechanical

injury inside the urethra. Moreover, reducing pain of experimental group may come from longer sustain of lubrication between the prostatectomy site, urethra injury site and Foley catheter than control group.

Limitations of this study were the relatively short follow-up and absence of animal study. We did not perform a power calculation Moreover the use of relatively large resectoscopic sheath may limit the generalizability of the findings reported in the present study. However, this is the first prospective, randomized controlled study to identify the usefulness of HA/CMC for reducing the incidence of post-TURP urethral stricture formation. Whether the efficacy of HA/CMC can be maintained persistently through long-term follow-up observations must be determined, and identification of the histological actions of the post-TURP use of HA/CMC requires animal studies.

Conclusion

The results of our study indicate that use of HA/CMC in the urethra during TURP decreases the incidence of urethral stricture. It showed effectiveness in reducing postoperative pain with no side effects, and improved patient satisfaction.

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Disclosures

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Figure legend

Figure 1. Instillation of HA/CMC on urethra using 18-gauze catheter

A: HA/CMC (5 mg) was instilled after TURP via an 18-gauze tube catheter.

B: After ballooning (to a volume of 30 cc) the urethral Foley catheter was pulled back to block the bladder neck. HA/CMC was then instilled between the urethral lumen and the Foley catheter.

C: A gauze was used to maintain traction for 1 day after surgery to retain the HA/CMC within the urethra.

Figure 2. The 26 weeks study with 2 weeks screening period and 24 weeks treatment phase

Figure 3. Surgical outcomes of the experimental group and the control group after TURP at each follow-up time point

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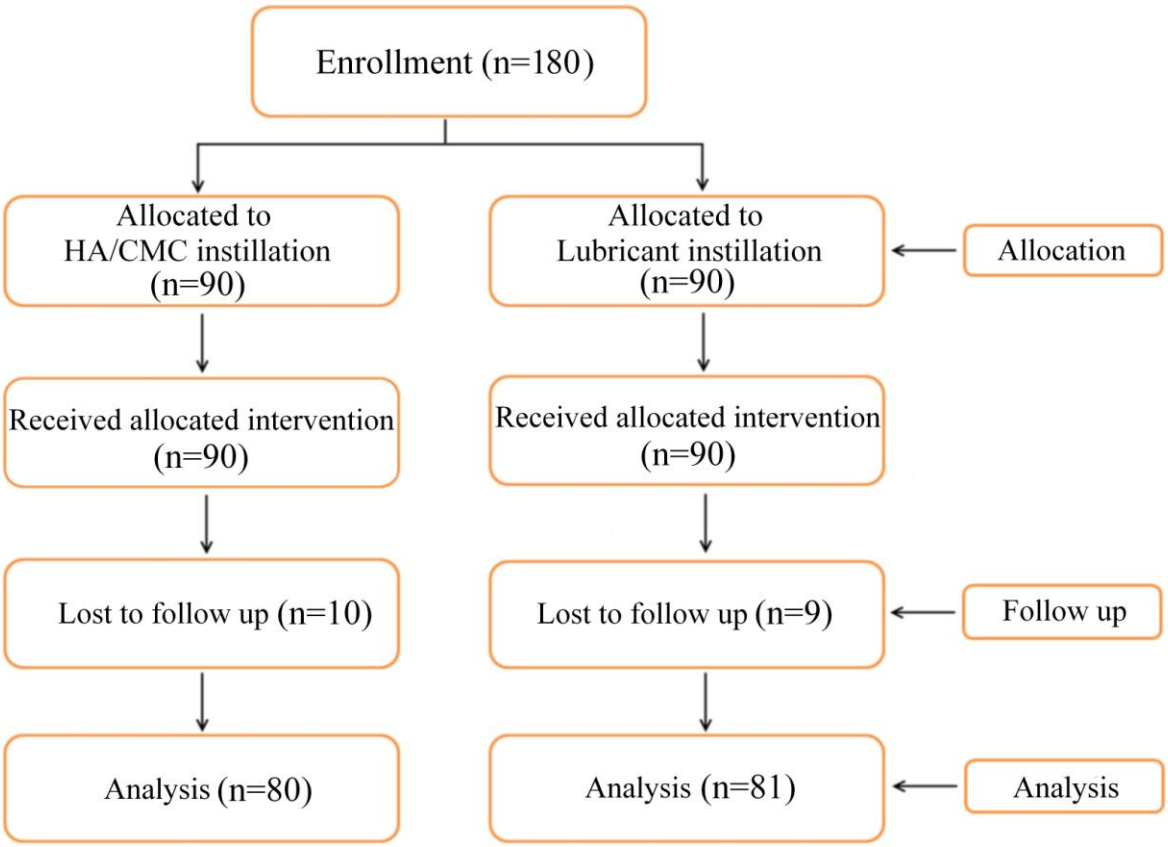
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Allocated to HA/CMC instillation (n=90)
Allocated to Lubricant instillation (n=90)
Allocation
Received allocated intervention (n=90)
Received allocated intervention (n=90)
Lost to follow up (n=10)
Lost to follow up (n=9)
Follow up
Analysis (n=80)
Analysis (n=81)
Analysis

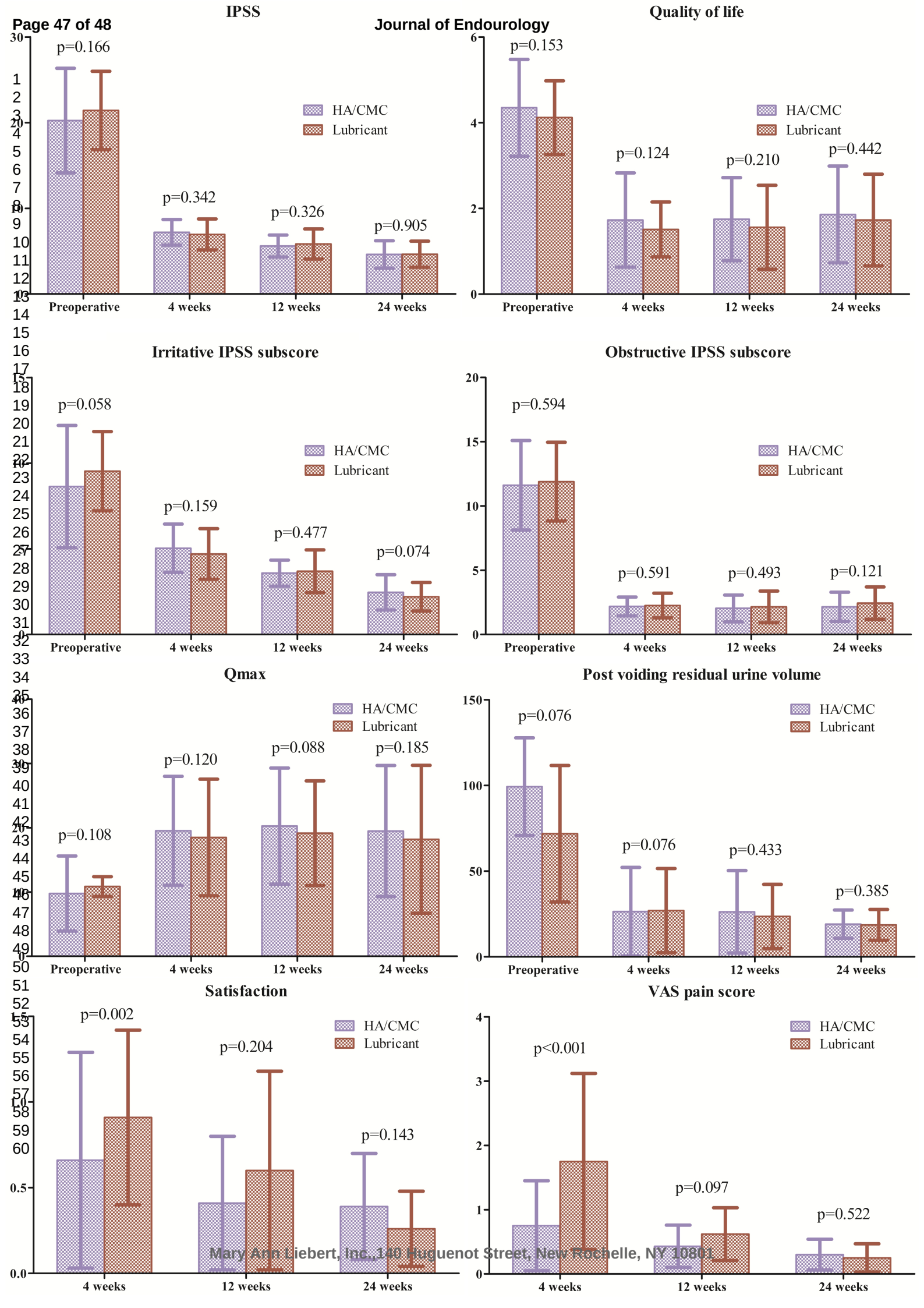

Table 1. Comparison of pre-, and perioperative variables between groups

		Group A (n=90)	Group B (n=90)	p-value
Preoperative				
Age, yrs		69.71±6.50	70.05±7.13	0.754
BMI, kg/m^2		25.26±2.57	24.75±3.63	0.306
PSA		2.66±2.75	2.92±2.52	0.523
TRUS	total volume, cm^3	49.77±22.57	52.78±22.35	0.396
	Transitional zone volume, cm^3	31.88±23.28	33.64±22.04	0.623
IPSS		20.24±6.10	21.42±4.58	0.166
	Irritative subscore	8.63±3.57	9.53±2.31	0.058
	Obstructive subscore	11.61±3.48	11.89±3.07	0.594
QoL		4.35±1.13	4.12±0.86	0.153
Qmax, mL/s		9.77±5.83	10.85±1.53	0.108
PVR, mL		99.31±28.49	71.91±39.81	0.076
Perioperative				
Resected prostate volume, cm^3		23.28±14.29	25.78±14.62	0.273
Catheter time, days		4.33±1.30	4.58±1.40	0.232
Hospital day, days		3.39±2.62	3.17±0.83	0.484

Student t-test
Group A : HA/CMC instillation, Group B : lubricant instillation
BMI: body mass index, PSA: prostate specific antigen, TRUS: transrectal ultrasonography, IPSS: international prostate symptom score, QoL: quality of life, Qmax: peak urine flow rate, PVR: post-voiding residual urine volume

Table 2. Complications

	Group A (n=80)	Group B (n=81)	p-value
Transfusion	0	1 (0.12%)	0.316
Capsule perforation	1 (1.25%)	0	0.322
Peri- and postoperative			
Clot retention	3 (3.75%)	2 (2.47%)	0.642
Transfusion	2 (2.50%)	0	0.154
Epididymo-orchitis	0	1 (0.12%)	0.322
Urethral stricture (by uroflowmetry)	9 (11.25%)	19 (23.46%)	0.041
Bladder neck contracture	0	0	
Urethral stricture (by urethrography)	1 (1.25%)	7 (8.64%)	0.031