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A prospective randomized trial of povidone-iodine suppository before transrectal ultrasonography-guided prostate biopsy

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Abstract

Objectives: To investigate a way to reduce infectious complication after transrectal ultrasonography-guided prostate biopsy (TRUS-Bx), we planned a randomized trial to determine whether the use of the povidone-iodine suppository is effective in preventing infectious complications.

Methods: This study prospectively assessed 250 patients who underwent TRUS-Bx during December 2014 and May 2016. Clinical questionnaire responses and safety were evaluated. Povidone-iodine suppository after glycerin enema was performed 1 to 2 hours before TRUS-Bx. Both groups received the prophylactic antibiotics (ceftriaxone 2.0 g) 30 to 60 minutes before TRUS-Bx. No antibiotics were prescribed after TRUS-Bx.

Results: The 120 were assigned in the treatment group using povidone-iodine suppository and 130 were assigned in the control group. There was no significant difference of clinicopathologic features including age, prostate-specific antigen and cancer detection rate in both groups ($P > .05$). No infectious and non-infectious complications were reported in both groups. Povidone-iodine suppository-related side effects were not reported. No significant differences in international prostate symptom score, sexual health inventory for men score, and European Organization for Research and Treatment of Cancer Quality of Life questionnaire scores were found between the 2 groups ($P > .05$). No changes in each questionnaire scores between before and after TRUS-Bx were observed.

Conclusions: Despite satisfying the predefined sample size, we could not prove the hypothesis that the use of povidone-iodine suppositories after TRUS-Bx would reduce infectious complications. A large-scale, multicenter, prospective study is needed to fully evaluate the clinical efficacy and safety of povidone-iodine suppository prior to TRUS-Bx.

Abbreviations: EORTX-QLQ-C30 = the European organization for research and treatment of cancer quality of life, IPSS = International Prostate Symptom Score, LUTS = lower urinary tract symptom, PSA = prostate-specific antigen, SHIM = sexual health inventory for men, TRUS = transrectal ultrasonography, TRUS-Bx = transrectal ultrasonography prostate biopsy.

Keywords: antibiotics, complication, povidone-iodine suppository, prospective randomized trial, prostate biopsy

1. Introduction

The number of prostate cancer cases is rapidly increasing among men; thus, the number of transrectal prostate biopsies for diagnosing prostate cancer is also rapidly increasing. As active surveillance for patients with low Gleason scores and prostate-specific antigen (PSA) levels shows an increasing trend, the incidence of transrectal prostate biopsy is expanding even more. In the decision-making process of men potentially facing a prostate biopsy, simple, noninvasive, objective parameters should be used, alone or in combination with prostate volume and, nevertheless, it is necessary to refer to nomograms in order to increase the accuracy of the biopsy.[1,2] Moreover, increasing role of biomarkers and multi-parametric magnetic resonance imaging (mpMRI) led to reduction of unnecessary biopsy and potential reclassification biopsy in active surveillance with prostatic biopsy.[3–5] This effort is important to reduce unnecessary testing because prostate biopsy is an invasive procedure and can lead to fatal consequences. In this sense, prevention of subsequent complications after transrectal ultrasonography-guided prostate biopsy (TRUS-Bx) became more important. Other studies have reported that infectious and non-infectious complications occurred (hematuria, urinary retention, etc.) in approximately 5% to 10% of patients after TRUS-Bx.[6] Infectious complications such as febrile urinary tract infections

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were observed in 4.2% to 5.1% of patients, requiring hospitalization in 81% to 100% of these patients, and in some cases, a severe clinical course such as sepsis may be observed.[7,8] Several attempts have been reported to reduce infectious complications after TRUS-Bx, including the use of antibiotics.[9–11]

We found that the use of rectal cleansing with povidone-iodine before TRUS-Bx could reduce the incidence of post-TRUS-Bx complications such as infection. Some studies reported that bowel preparation could reduce the incidence of infectious complications before TRUS-Bx. However, some studies reported opposite results.[12,13] Few retrospective studies and a small-sized prospective study reported that rectal cleansing with povidone-iodine could reduce the incidence of infectious complications during TRUS-Bx. However, these studies had the limitations of a small number of patients, selection bias, and retrospective nature. No prospective study has been conducted to clarify the effect of povidone-iodine suppository before TRUS-Bx.[14–16]

Povidone-iodine is widely used as a disinfectant for the prevention and treatment of wound infections, and the safety and usefulness of povidone-iodine suppositories especially in the field of gynecology have already been widely accepted.[17,18] Therefore, we investigated the prophylactic effect of povidone-iodine as a safe and proven-effective suppository before TRUS-Bx.

2. Materials and methods

We planned a prospective randomized trial of 276 patients who would be candidates for TRUS-Bx and were recruited from December 2014 to May 2016 at our institution. The patients were randomly assigned to the groups at a ratio of 1: 1 by clinical research coordinator. Of these patients, 26 patients were excluded owing to withdrawal from the trial (n = 6) and not performing prostate biopsy (n = 20). Finally, 250 patients were enrolled. To maintain the allocation concealment, the randomization table was placed in a sealed envelope, checked by a third party, and opened just before the patient was assigned. The patients were assigned to the treatment and control groups on the day of prostate biopsy. Before the procedure, the patients were divided into 2 groups, a treatment group (n = 120) with povidone-iodine suppository and a control group (n = 130) without suppository. Urinalysis, urine culture, and stool culture (rectal swab), demographic data (age, height, weight, and body mass index), complete blood count (CBC), admission panel, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) level, and thyroid function test were performed before TRUS-Bx. In addition, by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), International Prostate Symptom Score (IPSS) questionnaire, and Sexual Health Inventory for Men (SHIM) questionnaire, we evaluated the stability of the povidone-iodine suppository and the patient's symptoms before and after the procedure (Fig. 1).

All the patients received an intravenous injection of 2-g ceftriaxone 30 minutes to 1 hour before TRUS-Bx, and no additional antibiotic prescription was given thereafter. Before prostate biopsy, glycerin enema was performed to both groups approximately 3 hours before the biopsy. In the treatment group, 200 mg of povidone-iodine suppository was inserted 1 to 2 hours before the procedure. All transrectal prostate biopsies were performed as 12-core biopsies using an 18-gauge punch needle. Additional biopsy was performed up to a maximum of 4 cores if hypoechoic lesions were identified. One experienced radiologic expert performed the procedure to maintain the consistency of the TRUS-Bx.

The participants returned home without complications such as fever and bleeding after TRUS-Bx. No antibiotics were prescribed after TRUS-Bx. After TRUS-Bx, the body temperature from the eardrum was measured and recorded it twice before the first follow-up visit. The patients were interviewed for febrile complications and complications of the povidone iodine suppositories at the first follow-up visit and reevaluated using the questionnaires (SHIM, EORTC-QLQ-C30, IPSS total, IPSS QoL) before the TRUS-Bx.

The primary end point of this study was defined as the incidence of infectious complications such as fever and urinary tract infection within 1 to 2 weeks after TRUS-Bx. Infectious complication was defined as a tympanic membrane temperature $\geq$38.0°C within 3 days of prostate biopsy or as the case of visiting a medical institution for treatment due to high-fever symptoms. The exclusion criteria were hypersensitivity to povidone-iodine, thyroid dysfunction, renal failure, dermatitis, and radioiodine treatment.

According to the Cochrane Collaboration report that analyzed previously reported literature by meta-analysis, the incidence rates of infectious complications were 10% for fever, 14% for bacteriuria, 9% for urinary tract infection, and 18% for bacteremia.[6] Overall, infectious complications occurred in approximately 12.7% of the patients in the control group without antibiotics after prostate biopsy. The use of povidone-iodine prior to biopsy showed an approximately 80% reduction in complication rates (hazard ratio, 0.23; 90% confidence interval, 0.10–0.54) based on the meta-analysis reported by Pu et al[19] Therefore, 2.5% of infectious complications occurred in the povidone-iodine-treated group. When calculating the allocation ratio per group by 1:1 with 80% power (β value, 1–0.8 = 0.2) and 5% type 1 error (α value; false positive; 2-sided), 120 candidates were required in each group. Considering a dropout rate of 15%, 276 subjects were prospectively recruited.

To determine the clinical usefulness of povidone-iodine suppositories, we analyzed the incidence of infectious complications using cross tabulation and the chi-square test in comparison with those in the control group. A logistic regression univariate analysis was designed to analyze whether the administration of povidone-iodine suppository would be an independent predictor of the occurrence of infectious complications. Statistical analysis was performed on a per-protocol analysis basis, using the Statistical Package for the Social Sciences 22.0 software (SPSS Inc., Chicago, IL). A P value of $<.05$ was considered statistically significant. All these studies were conducted with institutional review board approval (IRB No. B-1403/243-004).

3. Results

In the treatment and control groups, the mean ages were 66.6 ± 8.6 and 65.2 ± 9.1 years; PSA levels, 12.6 ± 1.8 and 11.6 ± 3.2 ng/mL; number of biopsy cores, 12.9 ± 1.1 and 13.0 ± 1.2; and mean prostate volume, 42.4 ± 19.9 and 40.5 ± 17.2 mL, respectively (Table 1). The cancer detection rates (treatment group: 33.3% vs control group: 28.5%, $P = .100$) and the number of biopsy cores (treatment group: 12.9 ± 1.1 vs control group: 13.0 ± 1.2, $P = .159$) were not significantly different between the groups. The level of pre-biopsy CRP in both groups were 0.20 ± 0.54 and 0.19 ± 0.37 mg/dL, respectively (Table 1). Of the 250 patients, 74 (29.6%) patients were diagnosed with prostate cancer. (Gleason group 1–21 patients; group 2–25 patients; group 3–11 patients; group 4–15 patients; group 5–4 patients). Definition of Gleason group was based on International Society for Urological Pathology (ISUP) 2014 amendment.[20]

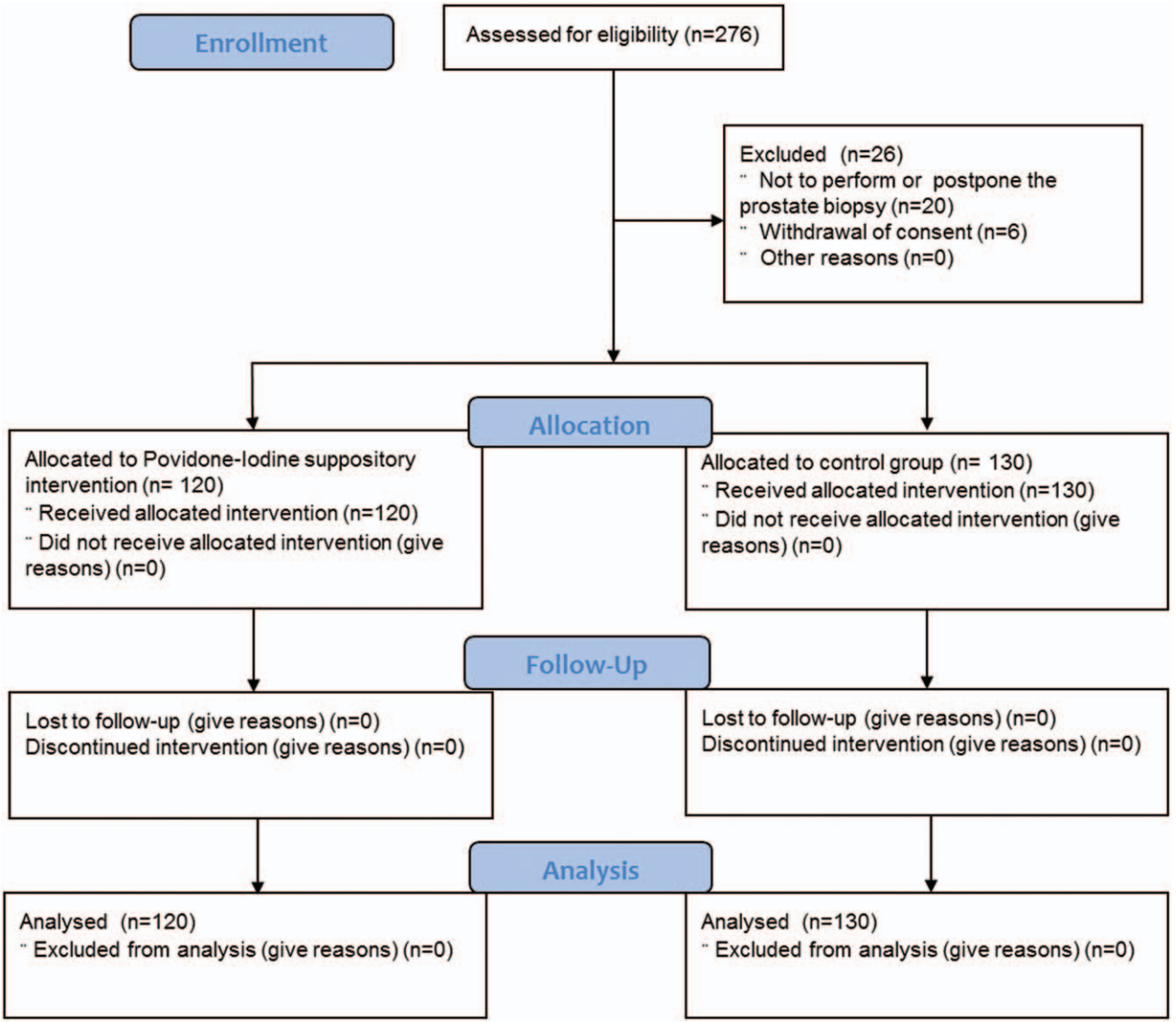

Figure 1. CONSORT 2010 flow diagram of the trial.

Table 1

Pre-biopsy characteristics of the total patients.

	Treatment group (n=120)	Control group (n=130)
Age, years	66.6±8.6	65.2±9.1
BMI (kg/m^2)	42.2±18.0	41.4±16.6
Pre-biopsy PSA level (ng/mL)	12.6±1.8	11.6±3.2
Prostate volume (mL)	42.4±19.9	40.5±17.2
Cancer detection rates (%)	33.3	28.5
Number of biopsy cores	12.9±1.1	13.0±1.2
Complications		
Infection	0	0
Bleeding	0	0
Severe pain	0	0
Other	0	0
Questionnaire scores		
SHIM	11.4±7.8	11.2±7.8
EORTC QLQ-C30	45.1±6.5	46.5±8.0
IPSS Total	10.0±6.8	11.0±7.0
IPSS: QOL	2.3±1.5	2.5±1.4
Nocturia	1.7±0.9	1.7±1.1

EORTC QLQ-C30 = the European organization for research and treatment of cancer quality of life, IPSS = International Prostate Symptom Score, SHIM = sexual health inventory for men.

Infectious complications did not occur in both groups, as well as any non-infectious complications such as bleeding and severe pain. Povidone-iodine suppository-related side effects were not reported in this study. No significant differences in IPSS, SHIM, and EORTC QLQ-C30 scores were found between the 2 groups ($P > .05$).

To examine povidone-iodine suppository-related side effects, we compared changes in questionnaire scores of the patient and control groups between pre-biopsy and post-biopsy (Table 3). The thyroid function test result after TRUS-Bx was within the normal range in both groups. Figure 2 shows the changes in questionnaire responses in both groups from before to after TRUS-Bx. The SHIM score of the treatment group was relatively higher than that of the control group and the post-biopsy decrease was relatively greater in the control group. The IPSS total and IPSS QoL scores were lower in the treatment group than in the control group and the post-biopsy score was higher in the control group than in the treatment group. The EORTC QLQ-C30 scores showed no significant change in both groups from

Table 2

Post-biopsy questionnaire scores of the 2 groups.

	Treatment group (n = 120)	Control group (n = 130)	*P* Value	95% confidential interval(CI)
Questionnaire scores				
SHIM	11.2 ± 7.8	10.28 ± 7.68	.490	0.958–1.021
EORTC QLQ-C30	45.1 ± 6.0	46.44 ± 8.25	.164	0.990–1.062
IPSS Total	10.0 ± 6.8	11.8 ± 7.0	.206	0.987–1.062
IPSS: QOL	2.2 ± 1.5	2.7 ± 1.4	.168	0.951–1.337
Nocturia	1.4 ± 1.0	1.6 ± 1.1	.119	0.611–1.106

EORTC QLQ-C30 = the European organization for research and treatment of cancer quality of life, IPSS = International Prostate Symptom Score, SHIM = sexual health inventory for men.

before to after TRUS-Bx but the treatment group showed lower scores than the control group. There was no significant change of CRP level of the patient (0.002 ± 0.250 mg/dL) and control groups (0.007 ± 0.330 mg/dL) between pre-biopsy and post-biopsy (*P* = .920, 95% CI -0.099–0.089). The nocturnal change in IPSS score showed the only significant decrease in the treatment group as compared with the control group (*P* = .036, 95% CI: 0.090–0.700) (Table 3). No abnormal thyroid function test results were found after TRUS-Bx in the treatment group.

4. Discussion

To our knowledge, the present study is the first prospective randomized trial to evaluate the clinical efficacy and safety of povidone-iodine suppository prior to TRUS-Bx. Many studies have shown that povidone-iodine bowel preparation could reduce the incidence of infection-related complications after TRUS-Bx. In a systematic review of 66 articles on infectious complications after TRUS-Bx, Walker et al reported that bowel preparation using povidone-iodine proved to be more effective in reducing post-TRUS-Bx infection.[21] In a meta-analysis reported by Pu et al, povidone-iodine bowel preparations also showed to be useful in preventing complicated infections.[22] In most of these studies, povidone-iodine solutions were used immediately prior to TRUS-Bx unlike in our study. Among the previous studies of suppository sanctions, most of those on povidone-iodine suppositories were performed in the field of gynecology and reported that povidone-iodine suppositories reduce vaginitis and postoperative infection rates.[17,18] As for the field of urology, povidone-iodine suppositories were reported to prevent infective complication after TRUS-Bx. However, these studies were limited owing to their retrospective design and small consortium.[23] We investigated the incidence of discomfort and lower urinary tract symptoms (LUTSs) between the treatment and control groups by using a symptom score survey and the incidence of infectious complications.

The protocol of administering adequate antibiotics and rectal preparations before performing TRUS-Bx has been widely accepted to reduce infection rates. However, the selection of antibiotics and regimen duration is controversial. According to the 2014 American Urological Association guideline, the recommended antibiotics for routine TRUS-Bx are fluoroquinolone, aminoglycosides, and first-, second-, and third-generation cephalosporins.[24] Among these antibiotics, the most widely used to date is fluoroquinolone, which can be used as an oral preparation. However, many quinolone-resistant bacteria have been reported in Korea and other Asian countries, and the use of quinolone has been reported to cause sole tolerance.[25,26] In addition, we previously reported that the use of third-generation cephalosporins is highly effective in reducing the risk of infectious complications as compared with the use of fluoroquinolone.[27] On the basis of these reports, we also used third-generation cephalosporins in this study. As a result, the absence of infectious complications in all 250 patients in the treatment and control groups in this study accounts for the superior prophylactic effect of third-generation cephalosporins.

As noted earlier, no infectious complication from using povidone-iodine suppositories was observed in both the treatment and control groups in this study. The 2 common prophylactic procedures applied in both groups were third-generation cephalosporin antibiotics and glycerin enema, in which the former is shown to be the more decisive factor in preventing infectious complications. In the study performed by Chung et al, the incidence rates of fluoroquinolone-resistant and extended-spectrum beta-lactamase production were 48.1% and 11.8%, respectively.[26] Recent reports also indicated that targeted antibiotic prophylaxis with rectal-culture screening may have significant benefits.[29] However, performing targeted rectal swab cultures has obvious difficulties depending on regions and institutions, making it clinically inevitable to use empirical antibiotics. In this regard, the present study proved that third-generation cephalosporin is an effective empirical prophylactic antibiotic that can be used prior to TRUS-Bx. However, since there was no control group that did not use third-generation cephalosporins, this study could not ultimately demonstrate that

Table 3

The change of questionnaire scores between pre- and post-biopsy setting.

	Treatment group (n = 120)	Control group (n = 130)	*P* Value	95% confidential interval(CI)
Questionnaire scores change				
SHIM	−0.5 ± 4.0	−1.0 ± 3.7	.302	−0.451–1.459
EORTC QLQ-C30	−0.1 ± 5.3	−0.1 ± 4.9	.936	−1.322–1.219
IPSS Total	−0.1 ± 4.8	0.8 ± 3.9	.176	−1.830–0.332
IPSS: QOL	−0.1 ± 0.9	0.1 ± 0.8	.375	−0.451–1.459
Nocturnal change	− 0.4 ± 0.8	− 0.1 ± 0.7	.036	0.090–0.700

EORTC QLQ-C30 = the European organization for research and treatment of cancer quality of life, IPSS = International Prostate Symptom Score, SHIM = sexual health inventory for men.

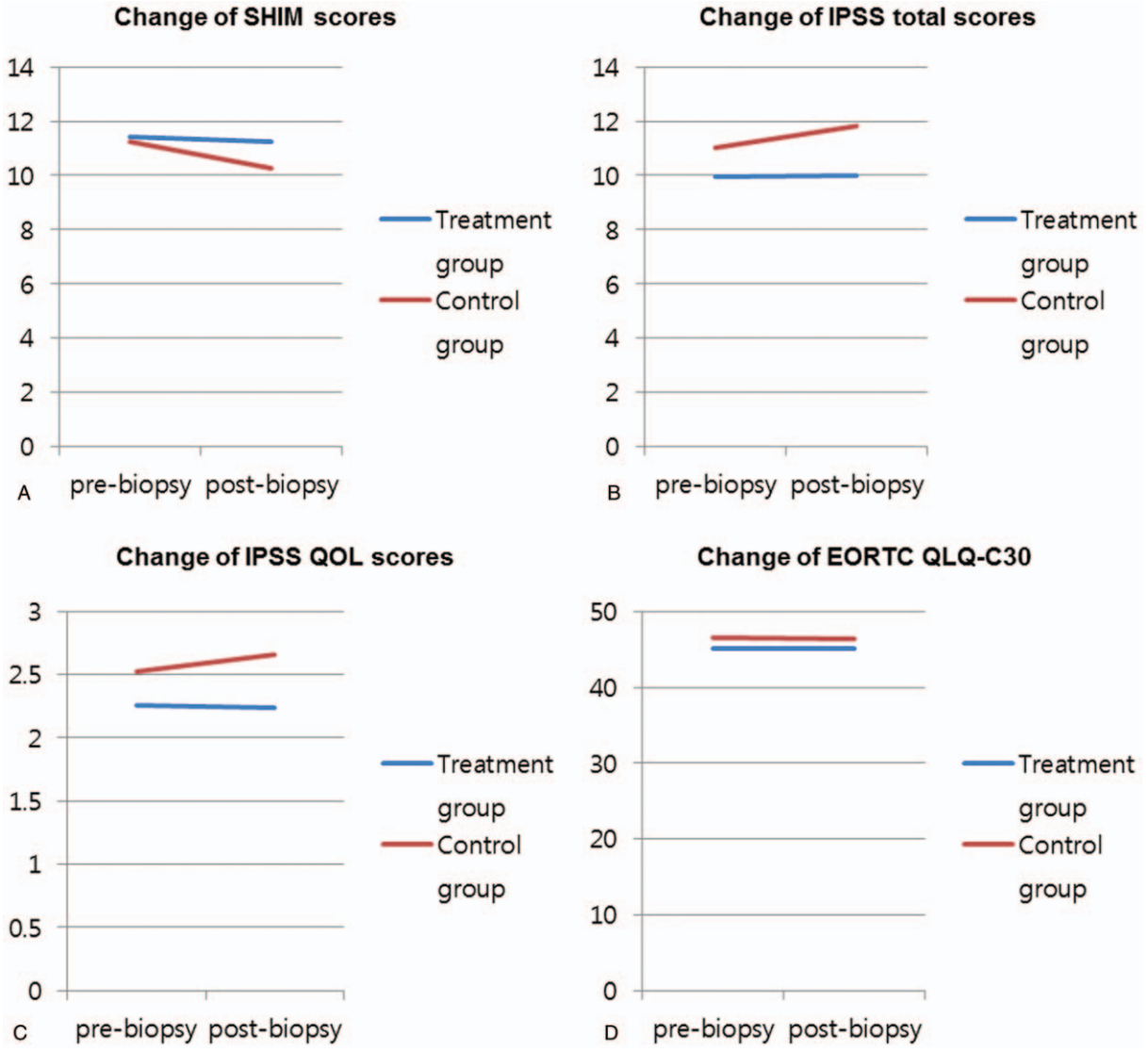

Figure 2. Changes in questionnaire scores in both groups from before to after TRUS-Bx.

third-generation cephalosporins are efficient at preventing post-TRUS-Bx infectious complications.

Aside from the fact that rectal preparation decreases the amount of feces in the rectum, thereby producing a superior acoustic window for prostate imaging, numerous studies have demonstrated that rectal preparation reduces the risk of infectious complications.[12,26] However, the point at which to begin rectal preparations is still unremarkable.[30] Some institutions perform enema 1 day prior to TRUS-Bx and restrict oral intake on the day of biopsy. In this study, we performed glycerin enema 4 hours prior to biopsy and restricted oral intake after the morning meal on the day of biopsy. As dietary restriction and bowel preparation prior to procedures are crucial to patient discomfort, while this study did not prove that bowel preparation alone can prevent infectious complications, it does demonstrate that with the proper antibiotic, minimal rectal preparation can be as effective with the least amount of discomfort to the patient in the process.

We surveyed patient discomfort and subjective complications between groups but found no statistically significant differences. When the average questionnaires scores were compared between the 2 groups, the statistical average scores for LUTS in the povidone-iodine suppository groups showed improvement as compared with those in the control groups. No previous studies have demonstrated that povidone-iodine can alleviate LUTS, and we deduced that the results were due to the placebo effect in the treatment group, assuming that the patients in the group were being provided better care with the additional use of suppositories. However, this also suggests that the suppository type does not increase patient discomfort as compared with the control. As previous cleansing with povidone-iodine has been reported to increase distress and irritation, this study demonstrates that the application of suppository types is effective in significantly lessening patient discomfort.[15]

Our study has limitations. First, it was conducted without a double-blinded method, thus the possibility of the patients in the treatment group to be under the impression of being provided better care with the povidone-iodine suppository than the control group, confounding the results of the survey. Second, the use of third-generation cephalosporins inadvertently interfered with the identification of the efficacy of povidone-iodine suppositories in infectious complications. As mentioned earlier, previous studies have mostly used fluoroquinolone as prophylaxis, and a research

on the efficacy of suppositories in patients with fluoroquinolone-resistant pathogens may have had more statistical significance. Other limitations include the selection bias of the homogeneity of the subjects chosen from a single institution, while antibiotic resistance is reported to be highly variable between regions. The limited number of enrolled patients also does not allow for sufficient analysis of patient discomfort and side effects due to suppository application. This is in part due to the primary intention of the study design to identify the statistical efficacy of povidone-iodine suppositories between the 2 groups, rather than the efficacy of the suppository itself. However, no evidence shows that povidone-iodine suppositories cause discomfort and irritation when applied in the rectum, and this study showed that the quality of life post TRUS-Bx was not affected by the use of the rectal medium.

Pre-biopsy rectal cleansing using povidone-iodine suppositories could not be demonstrated to reduce the rate of infectious complications because there was no infectious event despite our study satisfying the predefined sample size. A large-scale, multicenter, prospective study is needed to fully evaluate the clinical efficacy and safety of povidone-iodine suppository prior to TRUS-Bx.

Author contributions

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Funding acquisition: Sangchul Lee.
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