Original paper

Analysis of quality of life after randomized controlled trial of alpha-1 adrenoceptor antagonist alone and in combination with cyclooxygenase-2 inhibitor in patients who underwent low-dose-rate brachytherapy for prostate cancer

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Abstract

Purpose: The goal of this study was to evaluate the effect of cyclooxygenase-2 (COX-2) inhibitors on quality of life (QoL) of patients undergoing low-dose-rate (LDR) brachytherapy.

Material and methods: A total of 310 patients with prostate cancer who had undergone LDR brachytherapy were enrolled. The patients were randomized (1 : 1) to the monotherapy group (tamsulosin alone: 0.2 mg/day, n = 156) and the combination group (tamsulosin: 0.2 mg/day plus celecoxib: 200 mg/day, n = 154) without placebo. Using the expanded prostate cancer index composite (EPIC) and medical outcomes study 8-item short form health survey (SF-8) questionnaire, QoL was evaluated at baseline and at 1, 3, 6, and 12 months after seed implantation.

Results: The mean changes in scores from baseline to 1 and 3 months after seed implantation for the urinary (1M: –10.5, 3M: –10.9) and bowel (1M: –2.4, 3M: –4.2) domains of EPIC in the combination group were not significantly different from those (urinary 1M: –11.0, 3M: –11.4, bowel 1M: –2.3, 3M: –4.6) in the monotherapy group. The mean changes in scores from baseline to 1 and 3 months after seed implantation for the physical component summary (1M: 0.009, 3M: –0.32) and mental component summary (1M: 0.41, 3M: 0.36) of SF-8 in the combination group were not significantly different from those (physical component 1M: –0.89, 3M: –0.22, mental component 1M: 1.3, 3M: 1.1) in the monotherapy group.

Conclusions: Combination treatment with celecoxib and tamsulosin during the peri-operative period is not warranted for improving QoL in patients undergoing LDR brachytherapy.

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Key words: cyclooxygenase-2 inhibitor, low-dose-rate brachytherapy, prostate cancer, quality of life.

Purpose

Low-dose-rate (LDR) brachytherapy for prostate cancer has good oncological control, similar to radical prostatectomy and intensity-modulated radiation therapy (IMRT) in patients with low- and intermediate-risk [1,2,3]. Furthermore, a combination of external beam radiation therapy (EBRT) and LDR brachytherapy appears to have outcomes superior to those of surgery alone or EBRT alone in high-risk patients [1,2,3,4]. However, patients undergoing LDR brachytherapy have a lower QoL with respect to urinary, bowel, and sexual functions for 6 months after LDR brachytherapy [5,6]. Alpha-1 adrenoceptor antagonist administration significantly improves urinary symptoms in patients treated with LDR brachytherapy [7,8]. However, a low QoL is not sufficiently improved in patients taking alpha-1 adrenoceptor antagonist alone after LDR brachytherapy [9]. Therefore, we conducted a randomized controlled trial comparing alpha-1 adrenoceptor antagonist administration alone and in combination with cyclooxygenase-2 (COX-2) inhibitor in patients who had undergone LDR brachytherapy for prostate cancer, with a primary endpoint of change in the international prostate symptom score (IPSS)

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at 3 months after LDR brachytherapy [10]. In patients treated with COX-2 inhibitor, no change was observed in the IPSS, but daytime urinary frequency and post-void residual after seed implantation reduced.

If inflammation caused by LDR brachytherapy (needle insertion and seed implantation) or radiation lowers quality of life, anti-inflammatory agents could improve QoL. An *in vivo* study revealed that irradiation for bladder carcinoma causes pronounced COX-2 dependent inflammatory changes in the bladder wall, and that COX-2 inhibitors can decrease adverse events caused by radiation [11]. Feigenberg *et al*. retrospectively evaluated the efficacy of COX-2 inhibitors in patients with prostate cancer treated with brachytherapy, and found that treatment with COX-2 before brachytherapy significantly reduces urinary retention [12]. Furthermore, COX-2 inhibitor use improved the lowered QoL caused by radiation therapy in patients with nasopharyngeal carcinoma and breast cancer [13,14]. However, there is no study that evaluates the efficacy of COX-2 inhibitor in terms of QoL after LDR brachytherapy. Therefore, the present study aimed to focus on the additional impact of COX-2 inhibitor on QoL of patients undergoing LDR brachytherapy using the expanded prostate cancer index composite (EPIC) [15] and medical outcomes study 8-item short form health survey (SF-8) questionnaires [16].

Material and methods

Eligibility, registration, stratification, and randomization

Complete information on eligibility, registration, stratification, randomization, and the a priori statistical model has been provided in a previous publication discussing the change in IPSS [10]. The sample size was calculated (α: 0.05, β: 0.8, the mean difference of IPSS at 3 months after LDR brachytherapy in 2 groups: 2.5, standard deviation: 8.0) [6,17] and 162 patients were required for each group. A total of 360 patients with localized prostate cancer who had undergone LDR brachytherapy between May 2010 to July 2013 were enrolled in this open-labeled randomized controlled trial. Written informed consent was provided by 310 patients who were allocated to treatment with either tamsulosin alone (0.2 mg/day), or tamsulosin (0.2 mg/day) and celecoxib (200 mg/day) without placebo. This trial is registered with the UMIN Clinical Trials Registry as UMIN000003649. Treatment with tamsulosin began a day after brachytherapy started, and continued for at least 6 months after seed implantation or until the IPSS returned to the pretreatment score or lower, whereas celecoxib treatment was activated a day after brachytherapy started and continued for 3 months. The EPIC (disease-related QoL) and short form-8 (SF-8 health-related QoL) questionnaires were administered before seed implantation and at 1, 3, 6, and 12 months after seed implantation. The urologist who assessed the results of the questionnaires was not the same as the one who initiated the medication.

Radiation therapy

The prescribed dose of ^{125}I seed implantation alone was 160 Gy [18,19], whereas that in combination with EBRT was 110 Gy [18,19]. The clinical target volume for the LDR brachytherapy included the whole prostate. The implantation was based on peripheral loading technique with real time dynamic dose calculation using VariSeed® 8.0 (Varian Medical Systems, Palo Alto CA, USA). The target for the EBRT was determined 1 month after seed implantation, and the patients received 45 Gy (25 fractions, 1.8 Gy per fraction) using 10-MV photon energy and the three-dimensional conformal technique. The clinical target volume included both the entire prostate and the proximal third of the seminal vesicles. Post-implant dosimetry analysis was performed at 1-month post-seed implant.

Statistical analysis

Statistical analyses were carried out with PRISM software, version 7.00 (San Diego, CA, USA). A previous trial was powered according to the primary endpoint of change in the IPSS at 3 months after seed implantation. Secondary endpoints were QoL scores. Baseline patient and treatment characteristics were compared using the Chi-square test for categorical variables and the unpaired *t*-test was used for continuous variables. Changes in the QoL scores were calculated by subtracting the baseline score from the score at a designated time period for each patient. The mean change in scores was calculated for each time period. Statistically significant differences in the mean changes in scores for the urinary, bowel, hormonal, and sexual functions from the EPIC, physical component summary (PCS), and mental component summary (MCS) of the SF-8 questionnaires between the two treatment groups were assessed using an unpaired *t*-test.

Results

Patients who had provided written consent for the present trial were randomized to either the combination group (n = 154) or to the monotherapy group (n = 156). No adverse events related to COX-2 inhibitor use was observed, and no patient discontinued taking celecoxib due to adverse events. Moreover, no patient from the monotherapy group was administered celecoxib because of urinary disorders. There were no significant differences between the two groups with regard to patient background (Table 1) or post-implant dosimetry parameters (Table 2). The completeness of the EPIC and SF-8 data was excellent at 99.5% (1,543/1,550 points). There were no items with 5% or more values missing. There were no significant differences between the two groups in any domain, except for the physical domain score (p = 0.01) (Table 3).

For the urinary domain of EPIC, the mean change in scores from baseline to 1 month in the combination and monotherapy groups were –10.5 (standard deviation [SD]: ±11.7) and –11.0 (SD: ±15.3), respectively, and no significant difference was found between the two groups (p = 0.75). The mean change in scores from baseline to 3 months in the combination and monotherapy groups

Table 1. Patients characteristics

Variables	Combination group (n = 154)	Monotherapy group (n = 156)	P
	Median (range) or n		
Age (yrs)	70 (48-80)	70 (52-81)	0.91
PSA (ng/ml)	7.0 (3.7-43.6)	6.6 (1.2-41.7)	0.68
Prostate volume (ml)	22 (9-43)	22 (9-49)	0.18
Stage T1c/T2a/T2b/T2c/T3a	75/52/12/9/6	79/52/17/5/3	0.54
Gleason score 6/7/8-10	60/87/7	62/87/7	0.96
Neo ADT, yes/no	69/85	64/92	0.57
Duration of neo ADT (months)	4 (2-72)	4 (1-17)	0.07
EBRT, yes/no	55/99	56/100	1.00

Neo ADT – neoadjuvant androgen deprivation therapy, PSA – prostate-specific antigen, EBRT – external beam radiation therapy

Table 2. Post-implant dosimetry parameters

Variables	Combination group (n = 154)	Monotherapy group (n = 156)	P
	Median (range)		
$\%D_{90}$ (%)	122.5 (105-138)	121.6 (104-138)	0.44
D_{90} (Gy)	183.4 (107-221)	182 (124-217)	0.82
V_{100} (%)	99.2 (96-100)	99.1 (95-100)	0.69
V_{150} (%)	57.4 (32-78)	56.1 (34-74)	0.54
$\%UD_5$ (%)	137.4 (110-188)	136.2 (111-179)	0.67
UD_5 (Gy)	199.4 (126-300)	198.7 (127-277)	0.73
$\%UD_{30}$ (%)	125.5 (104-150)	125.1 (105-143)	0.69
UD_{30} (Gy)	187.2 (118-241)	184.7 (124-229)	0.86
$\%UD_{90}$ (%)	77.8 (26.1-123)	77.8 (24.5-119)	0.71
UD_{90} (Gy)	109.5 (31-184)	111.0 (28-1091)	0.55
R_{100} (ml)	0.01 (0.0-0.34)	0.00 (0.0-0.30)	0.99

$\%D_{90}$, D_{90} – minimal percentage of the dose and minimal dose (Gy) received by 90% of the prostate, V_{100}, V_{150} – percentage of the prostate volume receiving 100% and 150% of the prescribed minimal peripheral dose, $\%UD_5$, UD_5 – minimal percentage of the dose and minimal dose (Gy) received by 5% of the urethra, $\%UD_{30}$, UD_{30} – minimal percentage of the dose and minimal dose (Gy) received by 30% of the urethra, $\%UD_{90}$, UD_{90} – minimal percentage of the dose and minimal dose (Gy) received by 90% of the urethra, R_{100} – rectal volume (ml) receiving 100% of the prescribed dose

were –10.9 (SD: ±12.0) and –11.4 (SD: ±15.4), respectively, without a significant difference (p = 0.75). There was no significant difference between the mean change in scores from baseline to 6 months (p = 0.39, combination: mean –7.7, SD: ±11.4; monotherapy: mean –7.8, SD: ±16.2) or 12 months (p = 0.64, combination: mean –5.3, SD: ±15.1; monotherapy: mean –3.7, SD: ±14.9). The chronological changes in the subscales of the urinary domain are shown in Figure 1.

For the bowel domain of EPIC, the mean change in scores from baseline to 1 month in the combination and monotherapy groups were –2.4 (SD: ±7.9) and –2.3 (SD: ±8.2), respectively, and no significant difference was found between the two groups (p = 0.95). The mean change in scores from baseline to 3 months in the combination and monotherapy groups were –4.2 (SD: ±9.4) and –4.6 (SD: ±9.4), respectively, without a significant difference (p = 0.88). There was no significant difference between the mean changes in scores from baseline to 6 months (p = 0.77, combination: mean –3.5, SD: ±10.3; monotherapy: mean –3.9, SD: ±11.3) or 12 months (p = 0.28, combination: mean –3.7, SD: ±14.5; monotherapy: mean –2.2, SD: ±9.9). The chronological changes in the subscales of the bowel domain are shown in Figure 2.

For the hormone domain of EPIC, the mean changes in scores from baseline to 1 month in the combination and monotherapy groups were 0.80 (SD: ±7.9) and 1.42 (SD: ±7.9), respectively, and no significant difference was found between the two groups (p = 0.49). The mean change in scores from baseline to 3 months in the combination

Table 3. EPIC and SF-8 scores at baseline

Variables	Combination group (n = 154)	Monotherapy group (n = 156)	P
	M (SD)		
EPIC			
Urinary domain	96.0 (±5.2)	96.2 (±5.3)	0.74
Bowel domain	95.4 (±5.2)	95.6 (±5.8)	0.75
Hormone domain	93.0 (±7.5)	93.1 (±8.1)	0.91
Sexual domain	40.6 (±15.0)	39.0 (±12.5)	0.31
SF-8			
Physical function	48.6 (±6.9)	49.3 (±7.0)	0.38
Role physical	48.5 (±7.3)	50.4 (±5.9)	0.01
Bodily pain	53.0 (±7.5)	54.1 (±7.7)	0.20
Vitality	51.2 (±6.1)	51.8 (±6.5)	0.40
General health	50.0 (±6.0)	50.8 (±6.0)	0.24
Social functioning	49.6 (±7.5)	50.2 (±7.5)	0.48
Role emotional	49.3 (±6.2)	49.8 (±5.9)	0.47
Mental health	50.5 (±6.0)	50.8 (±6.1)	0.66
Physical component summary	49.4 (±6.3)	49.4 (±6.8)	0.99
Mental component summary	48.7 (±6.9)	50.1 (±6.5)	0.06

EPIC – expanded prostate cancer index composite questionnaire, SF-8 – medical outcomes study 8-item short form health survey questionnaire

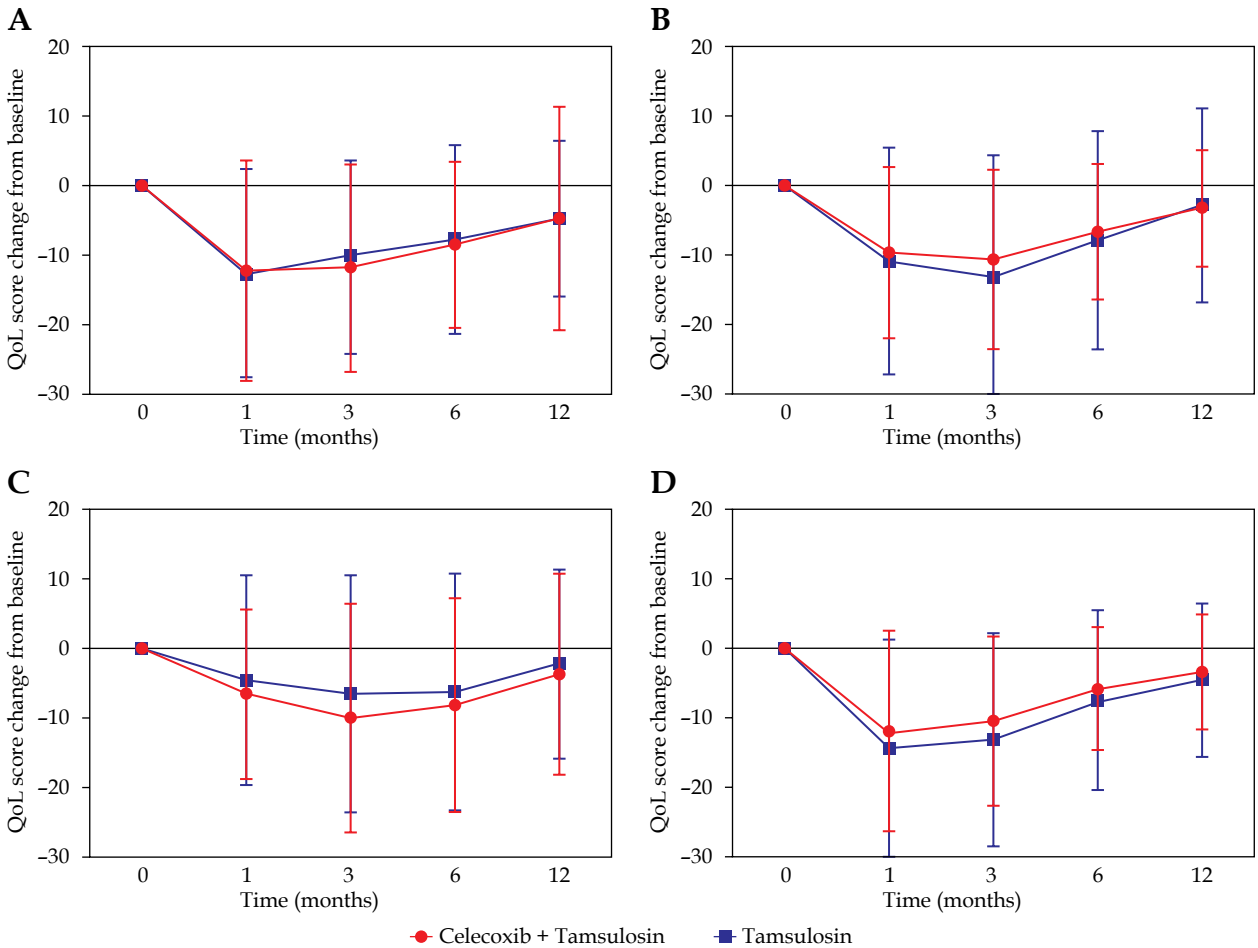

Fig. 1. Chronological changes in subscales of the urinary domain. **A**) Urinary function; **B**) Urinary bother; **C**) Urinary incontinence; **D**) Urinary irritative

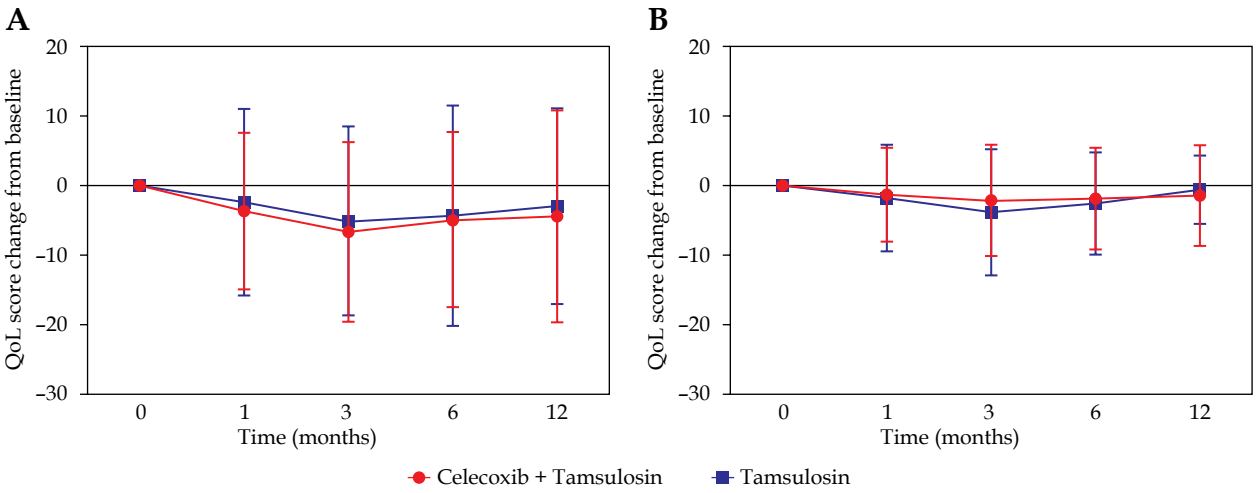

Fig. 2. Chronological changes in subscales of the bowel domain. **A**) Bowel function; **B**) Bowel bother

and monotherapy groups were 0.46 (SD: ±7.8) and 2.03 (SD: ±7.7), respectively, without a significant difference (p = 0.08). There was no significant difference between the mean change in scores from baseline to 6 months (p = 0.49, combination: mean 2.1, SD: ±10.1; monotherapy: mean 2.3, SD: ±8.5) or 12 months (p = 0.42, combination: mean 0.24, SD: ±16.4; monotherapy: mean 3.3, SD: ±8.4).

For the sexual domain of EPIC, the mean changes in scores from baseline to 1 month in the combination and monotherapy groups were –2.3 (SD: ±7.6) and –3.0 (SD: ±9.5), respectively, and no significant difference was found between the two groups (p = 0.47). The mean changes in scores from baseline to 3 months in the tamsulosin plus celecoxib and tamsulosin groups were –1.7 (SD: ±9.8) and –2.5 (SD: ±11.4), respectively, without a significant difference (p = 0.50). There was no significant difference between the mean changes in scores from baseline to 6 months (p = 0.46, combination: mean –1.5, SD: ±11.4; monotherapy: mean –2.0, SD: ±11.2) or 12 months (p = 0.66, combination: mean –1.8, SD: ±12.5; monotherapy: mean –1.3, SD: ±11.9).

For the PCS scores of SF-8, the mean changes in scores from baseline to 1 month in the combination and monotherapy groups were 0.009 (SD: ±7.2) and –0.89 (SD: ±7.9), respectively, and no significant difference was found between the two groups (p = 0.29). The mean changes in scores from baseline to 3 months in the combination and monotherapy groups were –0.32 (SD: ±6.8) and –0.22 (SD: ±7.2), respectively, without a significant difference (p = 0.90). There was no significant difference between the mean changes in scores from baseline to 6 months (p = 0.42, combination: mean –0.29, SD: ±8.4; monotherapy: mean –0.44, SD: ±8.8) or 12 months (p = 0.16, combination: mean –0.21, SD: ±9.8; monotherapy: mean –0.55, SD: ±9.3) (Figure 3G). For the bodily pain domain (Figure 3C), the mean changes in bodily pain from baseline to 1 month in the tamsulosin plus celecoxib and tamsulosin groups were –0.63 (SD: ±9.6) and 0.13 (SD: ±9.8), respectively. The mean changes at 3 months in the tamsulosin plus celecoxib and tamsulosin groups were –0.04 (SD: 9.8) and 0.38 (SD: 9.8), respectively.

For the MCS score of SF-8, the mean changes in scores from baseline to 1 month in the combination and monotherapy groups were 0.41 (SD: ±7.4) and 1.3 (SD: ±8.5), respectively, and no significant difference was found between the two groups (p = 0.32). The mean changes in scores from baseline to 3 months in the combination and monotherapy groups were 0.36 (SD: ±6.8) and 1.1 (SD: ±9.0), respectively, without a significant difference (p = 0.44). There was no significant difference between the mean changes in scores from baseline to 6 months (p = 0.41, combination: mean 0.77, SD: ±8.5; monotherapy: mean 1.3, SD: ±9.5) or 12 months (p = 0.27, combination: mean 0.13, SD: ±10.1; monotherapy: mean –1.7, SD: ±9.1) (Figure 3).

Discussion

The present randomized controlled trial was powered according to the primary endpoint (improvement of lower urinary tract symptoms [LUTS] in the IPSS), but the additional effect of the COX-2 inhibitor use on improving IPSS was not found [10]. Furthermore, in this study, no additional effect of COX-2 inhibitor use was found at 1, 3, 6, and 12 months after seed implantation for the urinary domain of EPIC. Crook et al. conducted a randomized trial to determine whether COX-2 inhibitor regimen initiated 1 week before seed implantation might diminish inflammatory response, and reduce edema, retention rates, and symptom severity. The study found that initiation of COX-2 inhibitor regimen 1 week before brachytherapy compared to initiation immediately after the procedure did not reduce 1-month edema, improve IPSS at 1 or 3 months, or reduce the need for catheterization [20]. Previous reports showed that addition of COX-2 inhibitor reduced daytime urinary frequency and post-void residual, which were secondary endpoints in this study [10]. However, QoL with regard to the urinary domain including IPSS, overactive bladder symptom score, and EPIC (urinary summary domain and subscales) did not improve on using COX-2 inhibitor. Furthermore, there was no significant effect of COX-2 inhibitor on urinary QoL in patients treated with LDR brachytherapy or with

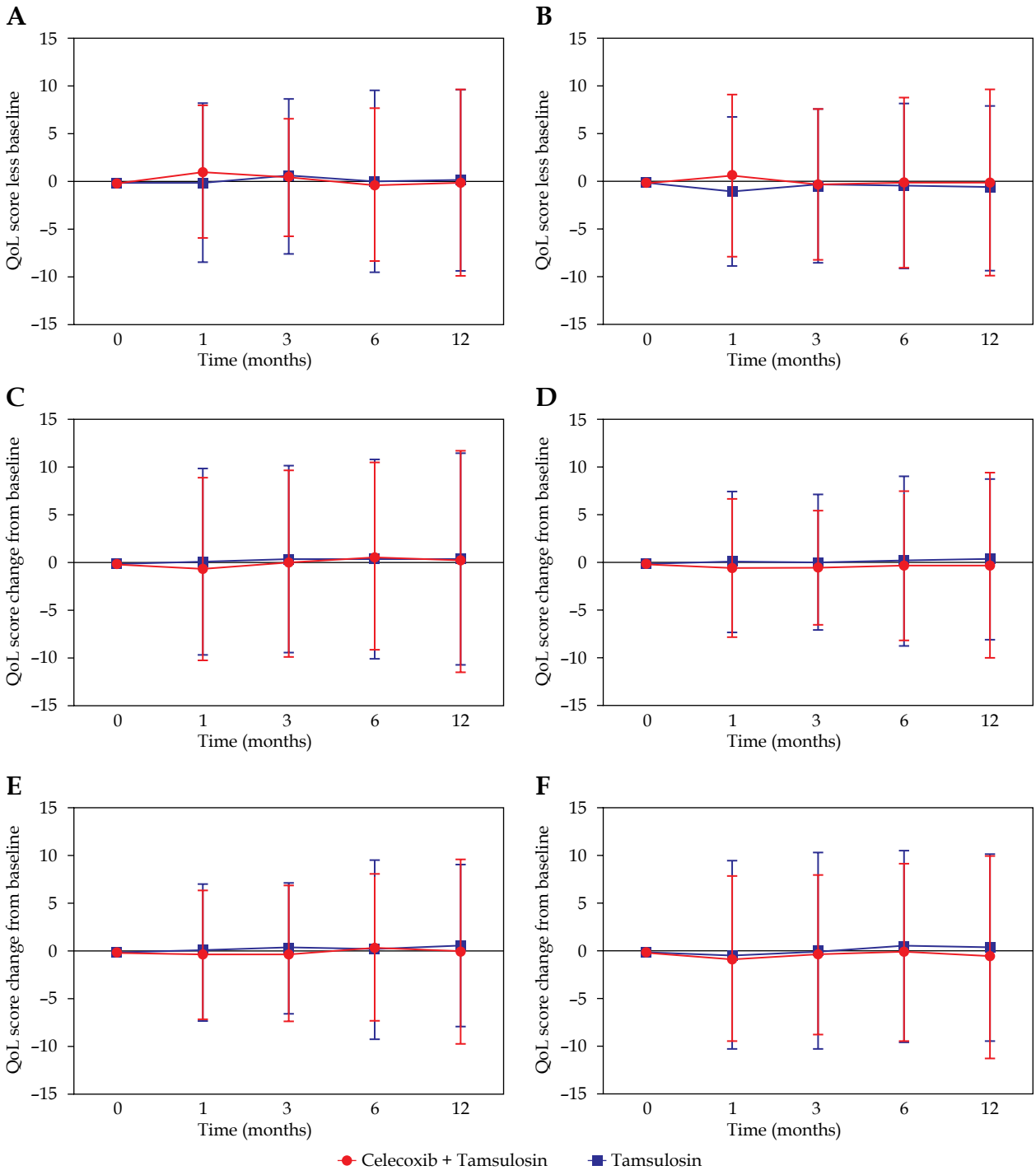

Fig. 3. Chronological changes in SF-8 scores. **A**) Physical function; **B**) Role physical; **C**) Bodily pain; **D**) Vitality; **E**) General health; **F**) Social functioning

LDR brachytherapy plus EBRT in the present study (data not shown), although urinary toxicities are different between LDR brachytherapy and LDR brachytherapy plus EBRT [5,21]. These results may indicate that the use of COX-2 inhibitor has an effect on urinary symptoms to some extent, but COX-2 inhibitor does not improve QoL in terms of the urination domain. That is, routine use of COX-2 inhibitor for LUTS during the perioperative period of brachytherapy is not warranted.

It is also reported in our other study that QoL for the bowel domain worsened in 37% patients treated with LDR brachytherapy alone and 68% patients treated with LDR brachytherapy plus EBRT within 3 months after LDR brachytherapy [5]. Although unlike IMRT, after the use of brachytherapy, QoL for the bowel domain improved after 24 months [5], a worse QoL in terms of the bowel domain is as important as that in terms of the urinary domain. If the lower QoL in terms of the bowel domain is

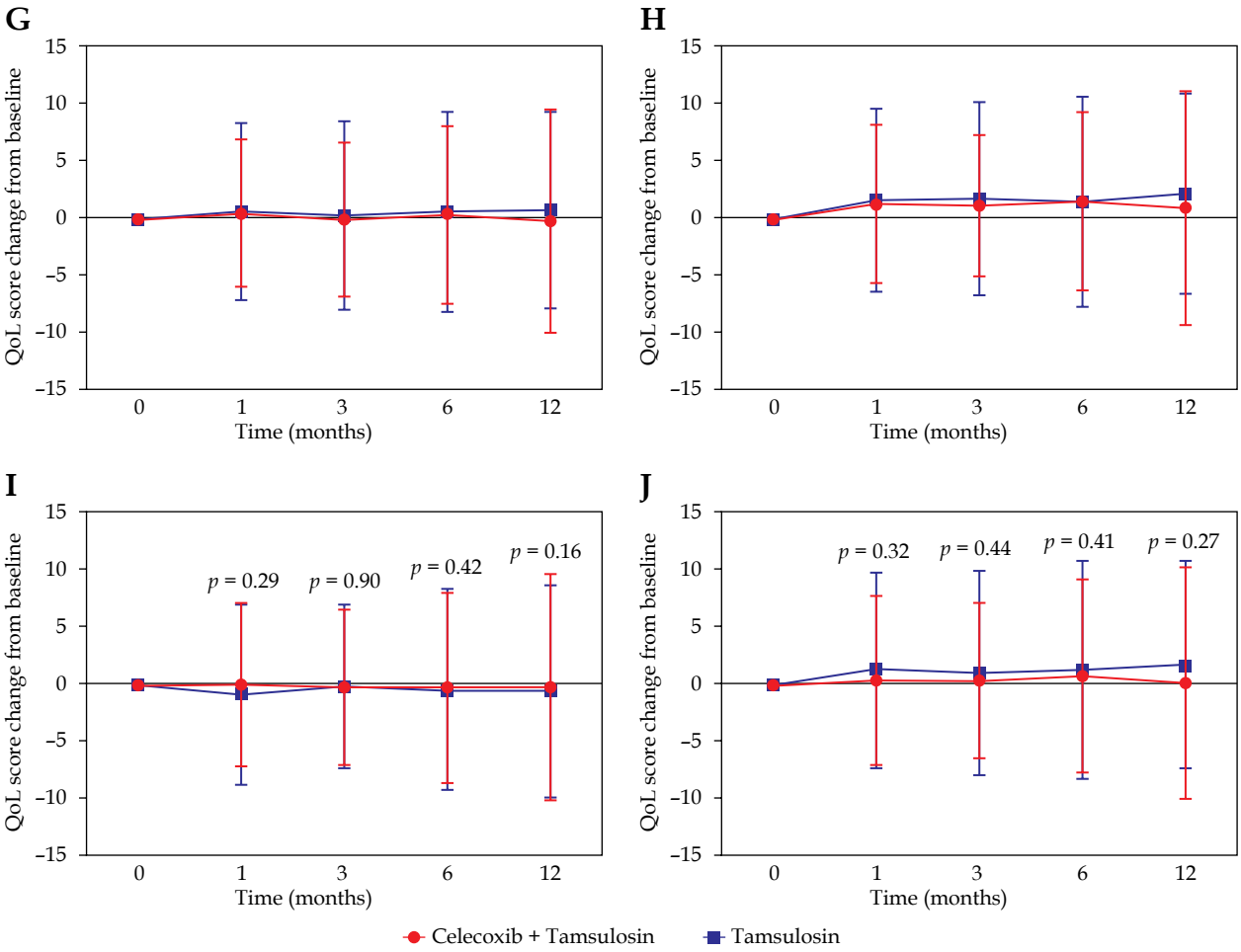

Fig. 3. Cont. **G**) Role emotional; **H**) Mental health; **I**) Physical component summary; **J**) Mental component summary

caused by inflammation due to a radiation effect, COX-2 inhibitor should be effective in resolving these adverse events. However, the present result showed almost the same changes in both groups (Figure 1B). These results indicate that routine use of COX-2 inhibitor to improve QoL in terms of the bowel domain during the peri-operative period of brachytherapy is not warranted.

Another concern is with regard to the analgesic efficacy of COX-2 inhibitor. In some reports, COX-2 inhibitor was found to relieve pain during peri-operative period; it was also found to improve QoL in a randomized controlled study [22]. Therefore, COX-2 should improve pain and physical and mental QoL. However, there was no significant difference found between physical and mental QoL upon combination therapy with the COX-2 inhibitor (Figure 3G and 3H). Furthermore, even in the bodily pain domain, there was no significant difference found with COX-2 inhibitor use (Figure 3C). These results indicate that routine use of COX-2 inhibitor to reduce pain during peri-operative period of brachytherapy is not warranted.

The present trial did not show efficacy of the COX-2 inhibitor in improving QoL within 12 months after seed implantation, which may be attributed to some reasons. The first reason is the timing of QoL evaluation. Gan *et al*. and Brattwall *et al*. reported the efficacy of COX-2 inhibitor in improving QoL within 7 days after laparoscopic cholecystectomy and elective hallux valgus surgery [19,23,24]. Brattwall *et al*. reported that 16 weeks after laparoscopic cholecystectomy, the efficacy of COX-2 inhibitor disappeared [24]. Given these findings, the COX-2 inhibitor may be effective in improving QoL immediately after surgery (within 7 days after the procedure), although the present trial did not evaluate QoL within 7 days after seed implantation. The second reason is that the dosage of COX-2 inhibitor (200 mg/day) may not be sufficient to improve QoL scores after seed implantation. Fan *et al*. reported the efficacy of celecoxib (400 mg/day) on QoL in patients treated with IMRT for nasopharyngeal carcinoma [13]. The third reason is that the expression of COX-2 in patients treated with LDR brachytherapy may be different from that in patients who were treated with a different variety of radiation therapy or surgery. However, the expression of COX-2 in patients after brachytherapy was not evaluated in the present study and this is one of the limitations of our study.

This study has also other limitations. First, it is an open-label trial and the results of QoL may be affected by the placebo effect. Second, the present trial was powered according to the primary endpoint (IPSS), and the objectives of the present report were the secondary endpoint.

Finally, compliance and adherence were not evaluated. Adherence was confirmed only verbally at a patient's visit.

Conclusions

Combination treatment with celecoxib and tamsulosin during peri-operative period is not superior to sole tamsulosin treatment for improving QoL in patients undergoing LDR brachytherapy.

Disclosure

The authors report no conflict of interest.

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