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Original Article

Optimisation of Radiation Therapy in Bladder Preservation Therapy for Patients With Clinical Stage T2N0M0 Bladder Cancer

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Abstract

Aims: A novel bladder preservation therapy, the OMC (Osaka Medical College) regimen, which combines radiation therapy with balloon-occluded arterial infusion of anticancer agents, is a treatment option for patients with muscle-invasive bladder cancer (MIBC). We retrospectively analysed the effects of changes in radiation dose and irradiation field on treatment efficacy and adverse events.The purpose of this study is to use the results of this study to help determine a course of radiation therapy for bladder preservation therapy of cT2N0M0 MIBC.

Materials and methods: We examined 352 patients with clinical stage T2N0M0 (cT2N0M0) MIBC classified into the following groups based on the irradiation method: group A, the whole pelvis (50 Gy/25 fractions) + local bladder (10 Gy/5 fractions); group B, the small pelvis (50 Gy/25 fractions) + local bladder (10 Gy/5 fractions); group C, the whole pelvis (40 Gy/20 fractions) + local bladder (10 Gy/5 fractions).

Results: The complete response rate, 3-year overall survival and progression-free survival rates in group A were 92.9%, 94.9% and 82.1%, respectively; in group B were 87.2%, 86.7% and 76.7%, respectively; and in group C were 95.2%, 92.6% and 71.1%, respectively. No significant differences between the groups were noted. The incidence of ≥grade 3 urinary tract and gastrointestinal toxicities were not significantly different among the groups (group A: 7.8%, 1.7%; B, 11.1%, 0%; C, 7.1%, 1.8%, respectively). The 3-year progression-free rates of the common iliac lymph node (CILN) region in patients who received whole-pelvis and small-pelvis irradiation were 99.0 and 89.0% ($P < 0.01$), respectively, with the latter group having significantly high lymph node recurrence in the CILN region.

Conclusions: Our findings showed that the optimal radiation therapy for patients with cT2N0M0 MIBC undergoing the OMC regimen is whole-pelvis irradiation including the CILN region, with a total dose of 50 Gy/25 fractions.

Key words: Balloon-occluded arterial infusion; bladder preservation therapy; invasive bladder cancer

Introduction

The standard treatment for muscle-invasive bladder cancer (MIBC) is total cystectomy; however, surgical resection inevitably results in a decreased quality of life. Recently, as a novel form of bladder preservation therapy (BPT), the combination of transurethral resection of bladder tumour (TUR-BT), chemotherapy and radiation therapy has been carried out in patients with MIBC, and a therapeutic effect comparable with total cystectomy has been reported [1–7]. BPT is one of the treatment options for elderly people for whom total cystectomy is not indicated because of their comorbidities, and for those who refuse cystectomy. The use of a trimodality combination therapy of TUR-BT, chemotherapy and radiation therapy has been reported to be important for BPT to achieve the maximum efficacy [8–12]. However, an optimal treatment method has not yet been established. In our institution, the OMC (Osaka Medical College) regimen (Figure 1) as BPT, which combines radiation therapy with balloon-occluded arterial infusion of anticancer agents, has been carried out. In the OMC regimen, the treatment strategy, such as irradiation dose and field, for cT2N0M0 MIBC has been adjusted sequentially over a 6-year period (Figure 2).

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To our knowledge, there have only been a few reports investigating the optimal irradiation dose and appropriate irradiation field for BPT. This study retrospectively examined the effects of changes in radiation dose and irradiation field on treatment efficacy and adverse events.

Subjects and Methods

Patient Selection

Of 480 patients with cT2N0M0 MIBC treated with radiotherapy (OMC regimen) at our institution between January 2013 and April 2019, 352 patients diagnosed with urothelial carcinoma underwent combined chemotherapy and completed radiotherapy. Figure 3 shows the patient exclusion and inclusion criteria. All cases were stage T2, N0 and the histology is high-grade urothelial carcinoma. The presence of hydronephrosis was also investigated and described. Overall, 23 patients had hydronephrosis.

Patients Treated with the OMC Regimen

Table 1 presents the baseline characteristics of the patients. There were 290 men and 62 women. The mean age was 67 years (range 29–85 years) at the initiation of the treatment. All patients were diagnosed with urothelial carcinoma. The median follow-up period was 34 months (7–88 months).

Radiotherapy Application

The patients were classified into three groups according to the method of radiation therapy: group A, the whole pelvis (50 Gy) + local bladder (10 Gy), with a total dose of 60 Gy/30 fractions; group B, the small pelvis (50 Gy) + local bladder (10 Gy), with a total dose of 60 Gy/30 fractions; and group C, the whole pelvis (40 Gy) + local bladder (10 Gy), with a total dose of 50 Gy/25 fractions (Figure 2). As an

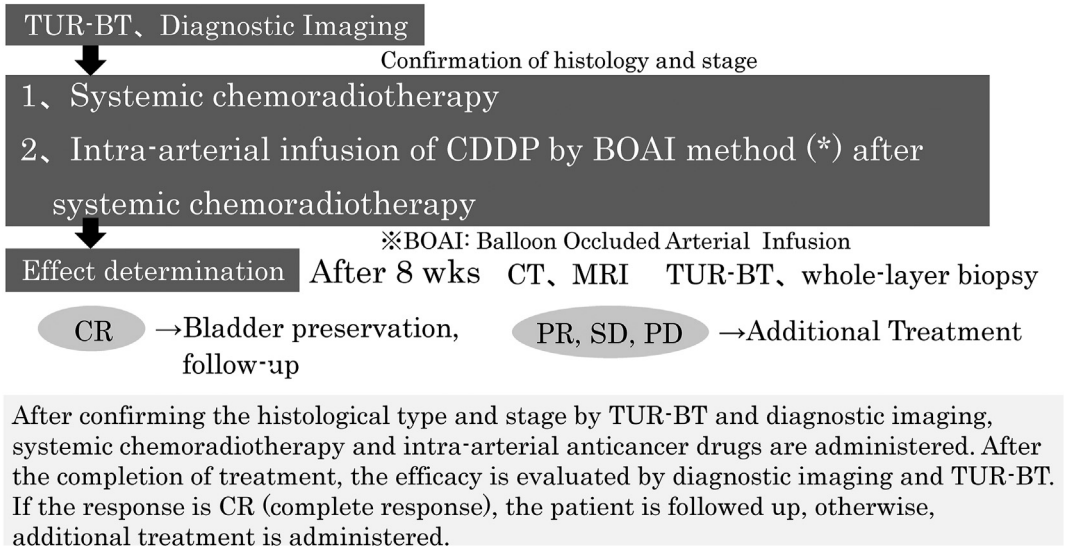

Fig 1. Our treatment policy for muscle-invasive bladder cancer.

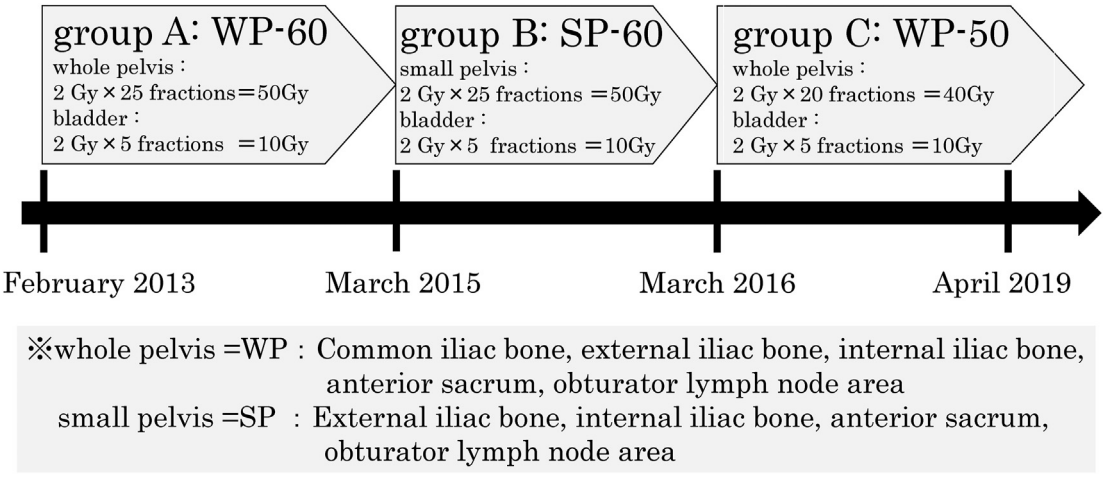

Fig 2. cT2N0M0 sequential transition of treatment strategy such as dose and range of irradiation in muscle-invasive bladder cancer.

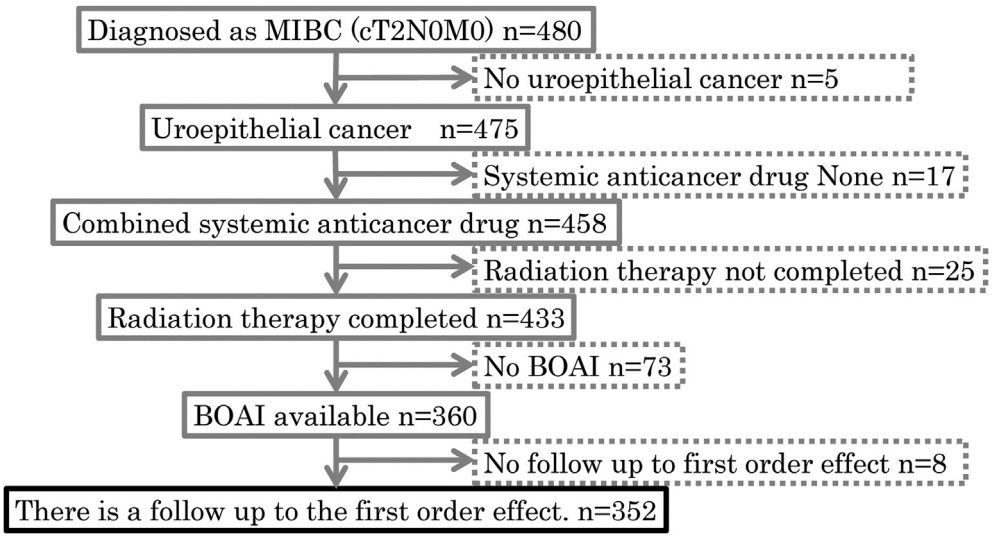

Fig 3. CONSORT flow diagram.

Table 1
Patients' characteristics

Number of patients			352
Male/female			290/62
Median age (years)[range]			67 [29–85]
Median follow-up period (months)[range]			34 [7–88]
Irradiation method (A/B/C)			126/39/187
Hydronephrosis (+/−)			23/329
	Group A	Group B	Group C
Number	126	39	187
Male/female	108/18	27/12	155/32
Median age (years) [range]	65 [29–84]	63 [38–83]	69 [47–85]
Median follow-up period (months) [range]	51 [9–88]	54 [8–66]	25 [7–53]
Hydronephrosis (+/−)	10/116	3/36	10/177

elective nodal area, the upper margins included the common iliac lymph nodes (CILN) in whole-pelvis irradiation and up to the bifurcation of the internal and external iliac arteries in small-pelvis radiation irradiation. There were 126 patients in group A, 39 in group B and 187 in group C. Patient characteristics for each of the three groups can be found in Table 1.

Chemotherapy

Systemic chemotherapy was administered simultaneously with radiotherapy. Gemcitabine (500 mg/m^2) and cisplatin (70 mg/m^2) were administered. Patients with a creatinine clearance of 45–60% had their anticancer agent dose changed to 70%, 30–45%–50% dose and those below 30% to Carboplatin. Gemcitabine was administered on days 1, 8 and 15 after radiotherapy started. Cisplatin was administered on day 2. Intra-arterial infusion of cisplatin (10 mg/body) was carried out using the balloon-occluded arterial infusion method immediately following systemic chemotherapy and radiation therapy Patients with a creatinine clearance of 45–60% were treated with dialysis, and under 45% were judged on an individual basis. Intra-arterial chemotherapy was administered only once. It was administered immediately after systemic radiotherapy and within 1 month after systemic chemotherapy. This regimen allows the anticancer agent to accumulate at very high concentrations at the tumour site, ensuring that the systemic concentration remains low.

Evaluation of the Therapeutic Effect

To determine the therapeutic effect, a complete response was defined as the clinical or pathological disappearance of the tumour based on contrast-enhanced computed tomography, magnetic resonance imaging or TUR-BT findings 3 months after the completion of radiation therapy. Pathological Tis (Carcinoma in situ) or Ta(noninvasive papillary carcinoma) remaining in TUR was included in the complete response. A tumour size reduction ≥30% (tumour size before the start of treatment was determined as the initial tumour size) was evaluated as a partial response, no change as stable disease and an increase ≥20% as progressive disease.

Outcomes

The response rate, overall survival, progression-free survival (PFS), recurrence pattern and incidence rates for adverse events (genitourinary and gastrointestinal tract) were compared between groups. The rate of progression free to the local bladder was defined as LPFR and the rate of progression free to the CILN region was defined as CILN-PFR. The curves in Figure 4b,c do not start at the 100% line, because the non-complete response group was counted as recurrence. If there were multiple recurrences at the same

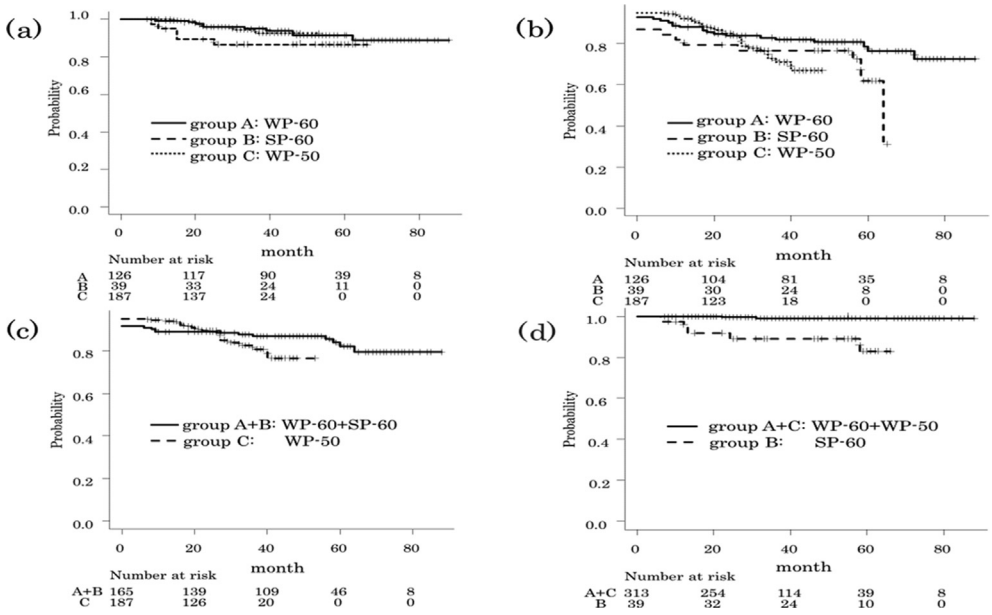

Fig 4. (a) Overall survival; (b) progression-free survival; (c) progression-free period (bladder); (d) progression-free period (common iliac lymph node).

time, they were counted in each event. For the evaluation of late adverse events, we counted those that occurred during the 2-year period in patients who could be followed for at least 2 years after treatment in order to match the evaluation criteria in three groups.

Statistical Analysis

Survival curves were analysed using the Kaplan–Meier method. The Log-rank test was used for statistical analysis and Fisher's exact test was used to analyse response rates and side-effects. The statistical analysis was carried out on the EZR software, version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Statistical significance was set at $P < 0.05$.

Ethics Approval

The study protocol was approved by the Intramural Ethical Review Committee of Osaka Medical and Pharmaceutical University (Osaka, Japan) (approval number: 2020-144; date of approval: 14 April 2021). We provided the enrolled patients with the opportunity to opt out on our website (https://www.ompu.ac.jp/u-deps/rad/houshasen-shuyou-research.html).

Results

Response Rate

In total, 117 (92.9%), 34 (87.2%) and 178 patients (95.2%) in groups A, B and C, respectively, showed a complete response. A partial response was observed in seven (5.6%), five (12.8%) and eight (4.3%) patients in groups A, B and C, respectively. Stable disease and progressive disease were observed in two (1.6%), zero (0%) and one (0.5%) patients in groups A, B and C, respectively (Table 2). There was no significant difference in response rate among the three groups.

Survival and Progression-free Period

The 3-year overall survival and PFS rates for group A were 94.9% and 82.1%, respectively; for group B were 86.7% and 76.7%, respectively; and for group C were 92.6% and 71.1%, respectively. There was no significant difference in overall survival and PFS among the three groups (Figure 4a, b).

Table 3 shows the number of patients with local recurrence and recurrence in the CILN region in each group. Local recurrence was 17 (13.5%), nine (23.0%) and 26 (13.9%) for groups A, B and C, respectively, and recurrence in the CILN area was zero (0%), five (12.8%) and two (1.1%), respectively. The 3-year LPFR in groups A + B (total radiation of 60 Gy to the bladder) and C (total radiation dose of 50 Gy to the bladder) were 86.9% and 80.7%, respectively. There was no

Table 2
Response rate

	CR	PR	PD
	n (%)	*n* (%)	*n* (%)
Group A: WP-60 ($n = 126$)	117 (92.9)	7 (5.6)	2 (1.6)
Group B: SW-60 ($n = 39$)	34 (87.2)	5 (12.8)	0 (0)
Group C: WP-50 ($n = 187$)	178 (95.2)	8 (4.3)	1 (0.5)

CR, complete response; PD, progressive disease; PR, partial response; SP, small pelvis; WP, whole pelvis.

Table 3
Recurrent form

	Bladder	Common iliac lymph node
	n (%)	*n* (%)
Group A: WP-60 ($n = 126$)	17 (13.5)	0 (0)
Group B: SW-60 ($n = 39$)	9 (23.0)	5 (12.8)
Group C: WP-50 ($n = 187$)	26 (13.9)	2 (1.1)

SP, small pelvis; WP, whole pelvis.

significant difference in the LPFR based on the radiation dose (Figure 4c). The 3-year CILN-PFR in groups A + C (the CILN area was irradiated) and B (the CILN area was not irradiated) were 99.0% and 89.0%, respectively. Recurrence in the CILN region was significantly higher in the non-irradiated group ($P < 0.01$) than in the irradiated group (Figure 4d).

Adverse Events

Late adverse events ≥grade 3 were evaluated only in patients who were followed up for more than 2 years (Table 4). Neither the urinary tract nor the gastrointestinal tract showed grade 4 or 5 late adverse events. The incidence of genitourinary toxicities of grade 3 in groups A, B and C were 7.8%, 11.1% and 7.1%, respectively, and there was no significant difference among the three groups. The incidence of gastrointestinal toxicities of grade 3 in groups A, B and C were 1.7%, 0% and 1.8%, respectively, and there was no significant difference among the three groups.

Discussion

Our findings indicate that in the OMC regimen, the complete response and 3-year overall survival rates of patients with cT2N0M0 MIBC were excellent, at about 90% each, with no significant difference noted between each group, regardless of the bladder radiation dose or irradiation field. Overall survival, PFS, bladder progression-free period and the incidence of late adverse events of the urinary and gastrointestinal tracts ≥grade 3 were not significantly different between the groups; only the progression-free rate of the CILN region was significantly reduced in the whole-pelvis irradiation group. In our institution, the BPT OMC regimen has been used since February 2013 in patients with MIBC who refused total cystectomy. At the beginning of treatment, the protocol included the same dose and irradiation field (50 Gy whole pelvis + 10 Gy local bladder for a total dose of 60 Gy/30 fraction) regardless of the presence of the T factor or pelvic lymph node metastasis. However, based on discussions with urological surgeons, in March 2015, the irradiation field was reduced to the small pelvis excluding the CILN region (a total dose of 60 Gy/30 fractions) in patients with cT2N0M0 cancer, because a large number of grade 2 or higher acute gastrointestinal disorders (diarrhoea) were observed. From March 2016, due to concerns about recurrence in the CILN area and occurrence of late adverse event of bladder, the irradiated area was re-expanded to the whole pelvis and the total dose was reduced to 50 Gy.

Table 4
Grade 3 late adverse events (patients under follow-up for more than 2 years)

	Urinary toxicity *n* (%)	Gastrointestinal toxicity *n* (%)
Group A: WP-60 ($n = 116$)	9 (7.8)	2 (1.7)
Group B: SP-60 ($n = 36$)	4 (11.1)	0 (0.0)
Group C: WP-50 ($n = 112$)	8 (7.1)	2 (1.8)

SP, small pelvis; WP, whole pelvis.

BPT combined with intra-arterial chemotherapy has been reported to have a complete response induction rate of 80–90% and an overall survival rate of 66–80% at 3–5 years [13–15]. Those of the OMC regimen were comparable or better than these rates. In this study, varying the radiation dose did not yield significant differences in treatment outcomes. However, considering the treatment duration and the risk of late toxicity, a total dose of 50 Gy/25 fractions may be preferable to 60 Gy/30 fractions for the OMC regimen. On the contrary, regarding the irradiation field, the recurrence rate in the CILN region was significantly higher in the non-irradiated group than in the irradiated group; thus, the irradiation of the entire pelvis was desirable. However, radiation therapy of the small pelvis may also be an option for patients with old age, poor performance status or a history of abdominal surgery.

The National Comprehensive Cancer Network guideline [16] recommends that the irradiation field for patients with MIBC should include the small pelvis as the regional lymph nodes, including the CILN region in patients with pelvic lymph node metastasis, and the additional irradiation of the entire or part of the bladder up to a total dose of 60–66 Gy.

The Massachusetts General Hospital reported that TUR-BT should be performed to remove the tumour, followed by the irradiation of the small pelvis area at a total dose of 40 Gy/22 fractions combined with chemotherapy. After 3 weeks, patient response should be evaluated. If there is residual disease, total cystectomy should be carried out. Otherwise, the irradiation area should be reduced to the bladder tumour only and an additional irradiation dose of 20–25 Gy/10–15 fractions should be prescribed [17]. The irradiation dose and field vary greatly depending on each guideline and remain unstandardised. Since the 1980s, the technology for the intra-arterial chemotherapy has been developed and has been applied to patients with bladder cancer in combination with radiation therapy [18]. In addition, the trimodality combination therapy with TUR-BT has recently been developed as a new form of BPT. Various studies [15,19–25] have reported radiation doses ranging from about 30 Gy to 60 Gy when radiation therapy is used in combination with intra-arterial chemotherapy; to date, the optimal dose remains unknown.

The rate of lymph node metastasis in patients with bladder cancer has been previously investigated using systematic dissection. One study recommended the inclusion of pelvic lymph nodes in the irradiation field as a prophylactic area [23–29]. On the other hand, there is a report that the significance of prophylactic irradiation to the lymph node irradiation has not been established because there was no difference in the frequency and survival rate of regional lymph node recurrence between the two groups of the presence or absence of prophylaxis to the lymph node area in a single-centre randomised controlled trial [2,30]. In concurrent chemoradiotherapy with an irradiation field including the pelvic lymph nodes at a dose of about 50 Gy, an increased incidence of gastrointestinal adverse events is of great concern. To date, there have been no randomised controlled trials investigating the irradiation field and whether whole-pelvis irradiation should be routinely carried out considering only the rate of lymph node metastasis has not yet been evaluated. BPT for patients with MIBC has not been standardised as a treatment method, and the treatment protocol differs across institutions. In addition, each institution that provides intra-arterial chemotherapy often irradiates below the recommended dose. To develop a therapeutic strategy, the balance between radiation therapy, systemic chemotherapy and intra-arterial chemotherapy should be considered. It is also necessary to confer with urinary surgeons. We believe that the results of this study will be useful in developing a standardised BPT protocol for radiation therapy in patients with cT2N0M0 MIBC. However, this study had some limitations. First, this study was retrospective and not randomised. Therefore, each treatment group had different sample sizes, patient characteristics and observation period; thus, the possibility of bias cannot be ruled out. In conclusion, in this study we retrospectively investigated the effects of changes in radiation dose and irradiation field on the treatment efficacy and incidence of adverse events of the OMC regimen in patients with cT2N0M0 MIBC. Although high complete response induction and survival rates were observed in all three groups, the results of this study suggest that irradiation including the entire pelvis area with a total dose of 50 Gy/25 fractions may be optimal. To develop an appropriate treatment strategy, a large cohort group should be investigated with a longer observation period. Randomised prospective trials should also be conducted in the future.

Conflict of interest

The authors declare no conflict of interest.

Author Contributions

MN is the guarantor of integrity of the entire study. MN, TS, KY and KN were responsible for study concepts and design. MN, TS and KN carried out the literature research. MN, AK, CS and AH were responsible for the clinical studies. MN, AK, CS, AH, JY and TS carried out the experimental studies/data analysis. MN, TS and KN carried out the statistical analysis. MN, HY, TS and KN prepared the manuscript. MN, HY, TS and KN edited the manuscript.

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