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ORIGINAL ARTICLE

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Lack of increase in postoperative complications with low-dose methotrexate therapy in patients with rheumatoid arthritis undergoing elective orthopedic surgery

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Abstract To determine the potential contribution of intermittent low-dose methotrexate (MTX) treatment (2–8 mg/week) to postoperative complications, we studied 122 patients with rheumatoid arthritis (RA) who had 201 surgical procedures. The patients with treatment with MTX were allocated to two groups: those who continued MTX (group A, 77 procedures) and those who discontinued MTX more than 1 week (group B, 21 procedures). The patients who had no treatment with MTX were allocated to group C (103 procedures). The incidence of postoperative infection, poor wound healing, and flare-up of RA was compared between the three groups. Postoperative infection occurred in 3.9%, 4.8%, and 3.9% in groups A, B, and C, respectively. Poor wound healing was experienced in 1.3%, 9.5%, and 7.8% in groups A, B, and C, respectively. At 4 weeks postoperatively, 3.9%, 14.3%, and 6.8% of flares were seen in groups A, B, and C, respectively. No significant difference was found in the patients with or without perioperative use of MTX. From these results, it is unlikely that continuation of intermittent low-dose MTX treatment increases the risk of postoperative complications in patients with RA. Continued treatment with MTX during perioperative period could suppress disease flares, especially in severe RA patients.

Key words Methotrexate (MTX) · Orthopedic surgery · Perioperative treatment · Postoperative complications · Rheumatoid arthritis (RA)

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Introduction

Methotrexate (MTX) is a folic acid antagonist that was originally used in high doses for treatment of malignancies. Methotrexate is prescribed in an intermittent low dose for the treatment of rheumatoid arthritis (RA)[1] and is recommended as the initial disease-modifying anti-rheumatic drug (DMARDs) because of its relatively rapid onset of action, its capacity to effect sustained improvement with ongoing therapy, and the high level of patient retention on therapy.[2,3]

Whether MTX should be continued or discontinued during the perioperative period has been controversial.[4] Previous studies using a small number of patients[5,6] and animal models[7] suggest that MTX may cause postoperative complications as a result of its immunosuppressive effects. In contrast, a prospective randomized study has recently demonstrated that perioperative use of MTX fails to increase wound infection or surgical complications such as rubor, discharge, wound dehiscence, or surgical revision.[8] Another retrospective analysis of RA patients who underwent hand surgery has also shown that MTX increases no statistically significant risk of wound infection.[9] Therefore, MTX could be continued to reduce flare-up of disease when optimal mobility is essential for effective rehabilitation.[4]

Compared with routine doses as approved in the United States (10–25 mg once weekly), the Japanese Ministry of Health, Labor and Welfare approves MTX for RA treatment in lower doses (2–8 mg/week), which may reduce the adverse effects of MTX. Currently, it remains obscure whether such low levels of MTX may affect the postoperative course. This retrospective study was aimed to determine the effects of perioperative use of MTX on complications after elective RA surgeries.

Patients and methods

We conducted a retrospective review of 124 RA patients who had undergone 206 elective orthopedic surgeries with a

total of 219 surgical procedures at Kyoto University during the period from January 2000 to December 2003. Surgeries for infection ($n = 2$) and those patients under treatment with etanercept ($n = 1$) or leflunomide ($n = 2$) were excluded from the study. As a result, 201 separate surgeries for 122 patients were identified with a total of 214 surgical procedures being performed. There was no patient who had been treated with infliximab. While many patients underwent multiple operations, 201 separate surgical episodes were identified with a total of 214 procedures being performed. The patients were classified into three groups. In group A, the patients had been given MTX (2–8 mg/week) at the Department of Orthopaedic Surgery and continued taking MTX perioperatively. In group B, the patients had been prescribed MTX (2–8 mg/week) at the Department of Clinical Immunology and MTX treatment was stopped more than 1 week during the perioperative period. Group C included patients with no history of MTX treatment.

Baseline features of the patients studied are summarized in Table 1, while associated chronic diseases and drug treatments in patients of the three groups are shown in Table 2. In groups A, B, and C, 83, 21, and 110 surgical procedures were performed, respectively. The details of surgical procedures are shown in Table 3.

Incidence of postoperative complications (infection and poor wound healing) and disease flares was compared in the three groups. All patients received prophylactic antibiotics perioperatively. Postoperative infection was defined as reddening of wound, discharge from the wound, and/or readministration of antibiotics occurring within 1 year after surgery, as described in the previous studies.[8] Samples for bacteriology were sent from the infections in six patients, resulting in four positive cultures. However, the negative culture report of two samples did not alter the definition of infection. Poor wound healing was defined as wound dehiscence after removal of suture. According to the definition of disease flares in the previous studies,[9] increase in pain in at least two joints with or without deteriorated morning stiffness of affected joints within 4 weeks after surgery indicates flare-up of RA.

Statistical analyses were done using the software, StatView Ver. 5 for Windows (Hulinks, Tokyo, Japan). Differences between age, RA disease duration, hematological data, and daily use of prednisolone were analyzed using one-way factorial analysis of variance, followed by Scheffe's test for multiple comparisons. Difference between continuation and discontinuance of MTX was analyzed by

Table 1. Baseline features of subjects in groups A–C

	Group A	Group B	Group C
No. of patients	48	12	56
No. of surgeries	77	21	103
Male	5	2	15
Mean age (years)	66	51	65
Range	(51–73)	(51)	(57–82)
Female	72	19	88
Mean age (years)	59	62	62
Range	(45–75)	(48–74)	(32–80)
RA disease duration			
Mean (years)	15	23	19
Range	(0.2–51)	(1–70)	(0.2–42)
CRP (mg/dl)	2.8	2.6	2.4
Alb (g/dl)	3.8	3.7	3.9
AST (IU/l)	19.5	23.2	20.3
ALT (IU/l)	15.5	20.9	16.2
BUN (mg/dl)	16.8	15.7	20.0
Cre (mg/dl)	0.60	0.60	1.07
Methotrexate			
Mean weekly dose (mg)	4.3	4.9	
Range	(2–8)	(2–8)	
Discontinuance of MTX			
1 week		11	
2 weeks		9	
>2 weeks		1	
Prednisolone			
Combination (%)	55 (71%)	13 (62%)	65 (63%)
Mean daily dose (mg)	5.7	8.9	4.8
Range	(2–20)	(2.5–15)	(2–10)

RA, rheumatoid arthritis; CRP, C-reactive protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; MTX, methotrexate

Table 2. Number of procedures associated with chronic diseases and drug treatment

	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Associated chronic disease						
Diabetes	7	9.1	0	0	6	5.8
Hypertension	16	20.7	11	52.4	42	40.8
Hypothyroidism	1	1.3	0	0	12	11.7
Liver cirrhosis	0	0	0	0	0	0
Chronic renal failure	1	1.3	1	4.8	10	9.7
Treatment						
NSAID	71	92.2	18	85.7	93	90.3
Gold	12	15.6	1	4.8	9	8.7
Bucillamine	23	29.9	2	9.5	27	26.2
Bredinin	0	0	0	0	3	2.9
Actarit	4	5.2	0	0	10	9.7
Penicillamine	0	0	0	0	2	1.9
Sulfasalazine	8	10.4	1	4.8	6	5.8
Cyclosporin	0	0	1	4.8	1	1.0

NSAID, nonsteroidal anti-inflammatory drug

Table 3. Surgical procedures

	Group A	Group B	Group C
Total joint arthroplasty			
Primary total hip arthroplasty	11	4	8
Revision total hip arthroplasty	2	1	2
Primary total knee arthroplasty	30	6	39
Revision total knee arthroplasty	4	1	2
Primary total elbow arthroplasty	6	3	14
Revision total elbow arthroplasty	0	0	2
Primary total shoulder arthroplasty	1	0	0
Subtotal	54 (65%)	15 (71%)	67 (61%)
Spine surgery			
Posterior fusion of cervical spine	6	2	8
Laminoplasty of cervical spine	0	1	1
Posterior fusion of thoracic spine	1	0	0
Posterior fusion of lumber spine	1	0	2
Fenestration of lumber spine	0	0	1
Discectomy of lumber spine	0	0	1
Others	1*[1]	0	0
Subtotal	9 (11%)	3 (14%)	13 (12%)
Hand surgery			
Synovectomy of elbow	0	0	3
Transposition of ulnar nerve	0	0	1
Synovectomy of wrist	1	0	1
Arthroplasty of wrist	2	1	0
Others	1	0	3*[2]
Subtotal	4 (5%)	1 (5%)	8 (7%)
Foot surgery			
Arthrodesis of ankle	3	1	7*[3]
Toe arthroplasty	13*[4–8]	1	13*[9–11]
Subtotal	16 (19%)	2 (10%)	20 (18%)
Others	0	0	2*[12]
Total	83	21	110

*[1]: Removal of spinal instrumentation with revision total knee arthroplasty
*[2]: Removal of instrumentation for internal fixation with arthrodesis of ankle
*[3]: Arthrodesis of ankle with primary total knee arthroplasty
*[4,5,10]: Toe arthroplasty with primary total elbow arthroplasty
*[6]: Toe arthroplasty with primary total knee arthroplasty
*[7,8,9,11]: Toe arthroplasty with arthrodesis of ankle
*[12]: Internal fixation of femoral fracture with revision total elbow arthroplasty

Student's *t*-test. Differences between the groups in the incidence of postoperative complications (infection and poor wound healing) or flare-up of RA were analyzed by Fisher's exact test. A logistic regression analysis was used to examine the effects of other clinical or therapeutic variables on the risk of postoperative complication (infection and poor wound healing) and flare-up of RA in the patients with treatment with MTX. A correlation between the dose of MTX and the flare was analyzed by Spearman's rank correlation coefficient. $P < 0.05$ was considered significant.

Results

Based on the data in Table 1, statistical analysis revealed that the disease duration in group B was significantly longer than that in group A ($P = 0.02$). The levels of blood urea nitrogen (BUN) and serum creatinine (Cre) in group C were significantly higher than those in group A ($P = 0.02$ and 0.05, respectively). The mean daily dose of prednisolone in group B was higher than that in group C ($P = 0.03$). Although statistical significance was not detected ($P = 0.06$), the mean age in group A was younger compared with that in group C. There was no significant difference in serum concentrations of albumin (Alb), aspartate aminotransferase (AST), or alanine aminotransferase (ALT) between the groups A–C. No difference was found between the mean weekly doses of MTX in groups A and B ($P = 0.13$).

Compared with group A, the incidence of patients with hypertension was high in groups B ($P = 0.02$) and C ($P = 0.02$). Hypothyroidism was more associated with the patients in group C than those in groups A and B ($P = 0.01$, and 0.05, respectively). There was no significant difference in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and other DMARDs between groups (Table 2).

Table 3 shows the details of surgical procedures. Eighty-four patients underwent more than one surgery during the period studied. Twelve patients received more than one surgical procedure at the same time of surgery. As a result, 201 separate surgeries with a total of 214 surgical procedures were performed. Fifty-four total joint arthroplasties,

9 spine, 4 hand, and 16 foot surgical procedures were performed in group A. Fifteen total joint arthroplasties, 3 spine, 1 hand, and 2 foot surgical procedures were performed in group B. Sixty-seven total joint arthroplasties, 13 spine, 8 hand, 20 foot, and 2 other surgical procedures were performed in group C.

Table 4 demonstrates the incidence of postoperative infection, poor wound healing, and flare-up of RA. Three postoperative infections were found in group A (3.9%), one in group B (4.8%), and four in group C (3.9%). Systemic infection was seen within 4 weeks after surgery (two each in groups A and C). Bacteriological examination of six samples yielded four positive cultures. Statistical analyses revealed no significant difference in the incidences of infection between the groups. While poor wound healing was found in one, two, and eight procedures in groups A (1.3%), B (9.5%), and C (7.8%), respectively, no statistically significant difference was found in the incidence between the groups. Flare-up of RA was seen in three, three, and seven procedures in groups A (3.9%), B (14%), and C (6.8%), respectively, without significant differences between the groups.

Factors influencing the risk of postoperative infection and poor wound healing in the RA patients of groups A and B were investigated by logistic regression analysis (Tables 5 and 6). Perioperative use of MTX failed to correlate with the risk of these postoperative complications. While the analysis showed significant association between the weekly doses of MTX and postoperative infection ($P = 0.04$, Table 5a), no infection was seen even in the patients who took 6–8 mg/week of MTX (Table 5b). The daily dose of prednisolone increased the risk of postoperative infection, although there was no statistically significant difference ($P = 0.06$, Table 5a). No factor correlated with poor wound healing (Table 6).

Factors associated with disease flares in the patients of groups A and B were also investigated by logistic regression analysis (Table 7). The analysis clearly demonstrated that the flare-up of RA correlated with discontinuance of MTX as well as high levels of C-reactive protein (CRP) before surgery. There was a significant correlation between the flares and treatment with gold and actarit ($P = 0.04$ and 0.05, respectively). The analysis using both groups A and B showed no association between the flares and weekly dose of MTX. However, flare-up of RA significantly correlated with the weekly dose of MTX in group B ($P = 0.01$, Table 8). In contrast, there was no correlation between the disease flares and weekly dose of MTX in group A (Table 8).

Discussion

The main purpose of this study was to compare the risk of postoperative complications and flare-up between perioperative continuance and discontinuance of MTX

Table 4. Incidence of postoperative infection, poor wound healing, and flare-up of RA

	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Postoperative infection	3	3.9	1	4.8	4	3.9
Systemic infection	2		0		2	
Culture obtained	3		1		2	
Positive culture	3		0		1	
Poor wound healing	1	1.3	2	9.5	8	7.8
Flare-up of RA	3	3.9	3	14.3	7	6.8

Table 5b. Correlation between postoperative infection and weekly dose of MTX in patients of groups A and B

MTX (mg/week)	2	3	4	5	6	8
Surgery (total)	15	2	49	5	21	6
Group A	11	0	44	5	15	2
Group B	4	2	5	0	6	4
Infection (total)	1	0	1	2	0	0
Group A	0	0	1	2	0	0
Group B	1	0	0	0	0	0

Table 5a. Analysis of postoperative infection in patients of groups A and B: logistic regression analysis

	P value	Odds ratio	95% confidence interval
Baseline features of RA patients			
CRP before surgery (mg/dl)	0.24	0.31	0.04–2.2
RA duration (years)	0.28	0.80	0.53–1.2
Treatment			
Discontinuance of MTX	0.42	0.01	4.3×10^{-8}–1.1×10^{3}
Weekly dose of MTX (mg)	0.04	0.07	0.5×10^{-2}–0.9
Daily dose of prednisolone (mg)	0.06	1.9	1.0–3.9
Gold	1.0	1.9×10^{-9}	0.00
Actarit	1.0	4.4×10^{-9}	0.00
Sulfasalazine	1.0	1.9×10^{-7}	0.00
Cyclosporin	1.0	0.1×10^{-2}	0.00
NSAID	0.24	2.7×10^{-4}	3.3×10^{-10}–2.1×10
Intercurrent disease			
Diabetes	1.0	4.8×10^{-7}	0.00
Hypertension	0.07	1.3×10^{5}	0.39–0.41×10^{11}
Chronic renal failure	0.07	2.6×10^{3}	0.5–1.3×10^{7}
Operation time (min)	0.11	1.1	0.99–1.1

Table 6. Logistic regression analysis of poor wound healing in patients of groups A and B

	P value	Odds ratio	95% confidence interval
Baseline features of RA patients			
CRP before surgery (mg/dl)	0.84	0.86	0.2–3.7
Alb (g/dl)	0.43	7.1×10^{-6}	1.3×10^{-13}–4.0×10^{7}
RA duration (years)	0.81	0.96	0.68–1.3
Treatment			
Discontinuance of MTX	0.84	0.4	5.2×10^{-5}–3.1×10^{3}
Weekly dose of MTX (mg)	0.51	0.35	1.5×10^{-2}–8.2
Daily dose of prednisolone (mg)	0.74	0.75	0.13–4.2
Gold	1.0	4.1×10^{-8}	0.00
Bucillamine	1.0	6.5×10^{-8}	0.00
Actarit	1.0	43	0.00
Sulfasalazine	1.0	2.0×10^{-3}	0.00
NSAID	0.48	0.09	1.3×10^{-4}–67
Intercurrent disease			
Diabetes	1.0	0.5×10^{-2}	0.00
Hypertension	1.0	4.2×10^{10}	0.00
Hypothyroidism	1.0	0.55	0.00
Operation time (min)	0.61	0.9	0.72–1.2

Table 7. Logistic regression analysis of flare-up of RA in patients of groups A and B

	P value	Odds ratio	95% confidence interval
Baseline features of RA patients			
BMI	0.29	1.41	0.74–2.6
CRP before surgery (mg/dl)	0.04	0.19	0.04–0.9
Alb (g/dl)	0.23	0.7×10^{-2}	2.7×10^{-6}–21
RA duration (years)	0.12	0.85	0.69–1.0
Treatment			
Discontinuance of MTX	0.03	5.0×10^{3}	2.0–1.3×10^{7}
Weekly dose of MTX (mg)	0.14	2.8	0.72–11
Daily dose of prednisolone (mg)	0.24	0.71	0.46–1.3
Gold	0.04	2.0×10^{3}	1.3–3.1×10^{6}
Bucillamine	0.47	0.13	0.1×10^{-2}–32
Actarit	0.05	2.2×10^{3}	1.2–4.1×10^{6}
Sulfasalazine	1.0	6.4×10^{-7}	0.00
Cyclosporin	1.0	5.5×10^{-13}	0.00
NSAID use	1.0	1.8×10^{10}	0.00
Intercurrent disease			
Diabetes	1.0	0.1×10^{-2}	0.00
Hypertension	0.93	0.83	0.01–48
Hypothyroidism	1.0	1.7×10^{-9}	0.00
Operation time (min)	0.06	1.0	1.0–1.1

BMI, body mass index

Table 8. Correlation between the flare-up and the dose of MTX in patients of groups A and B

MTX (mg/week)	2	4	5	6	8
Group A					
Surgery	11	44	5	15	2
Flare-up (+)	0	3	0	0	0
MTX (mg/week)	2	3	4	6	8
Group B					
Surgery	4	2	5	6	4
Flare-up (+)	0	0	0	2	1

therapy in 122 patients with RA who underwent elective orthopedic surgery. In our retrospective study, logistic regression analysis indicates that discontinuance of MTX, especially at high doses, increases flare-up of the disease. Compared with discontinuance of MTX, perioperative use of MTX is unlikely to increase the incidence of postoperative infection and poor wound healing.

In the 1990s, continued treatment with MTX (mean: 8.1 mg/week) was found to increase the incidence of infection in RA patients, compared with no complications in patients without MTX treatment within 4 weeks of surgery,[5] while no flares of RA were found after MTX (mean: 12.7 mg/week, range: 5–20 mg/week) withdrawal among the patients taking MTX for 2 weeks.[6] These results, which are incompatible with our current findings, were widely interpreted as suggesting that MTX should be discontinued

before surgery. However, these studies relied on a relatively small number of patients.

In contrast, two recent reports support our findings. The prospective randomized study of 388 RA patients undergoing elective orthopedic surgery has shown that continuation of MTX (mean: 8.9 mg/week, range: 2.5–20 mg/week) throughout the perioperative period is not associated with an increase in either wound infection or complications and that it reduces the incidence of disease flares within the first year after surgery.[8] Another retrospective study of 80 RA patients who had 129 surgical procedures on the hand and wrist over a 5-year period has demonstrated that there is no increased risk of wound infection or breakdown with treatment with MTX (mean: 10 mg/week, range: 2.5–25 mg/week) during the perioperative period.[9]

In the two recent studies described above, the factors influencing the postoperative complications have never been analyzed in the groups of patients with and without perioperative use of MTX. The logistic regression analysis of such groups in our present study found no statistically significant factors influencing postoperative infection and poor wound healing. Although discontinuance of MTX had little effect on those postoperative complications, it caused an increase in disease flares within 4 weeks after surgery. C-reactive protein before surgery was also associated with flares. Further analyses of flares in the group of patients who perioperatively received MTX showed no significant correlation between flares and weekly doses of MTX. In contrast, discontinuance of higher doses of MTX resulted in a higher incidence of flares in the group of patients without perioperative use of MTX.

It remains unclear how long perioperative use of MTX may affect the postoperative course. Thus, an appropriate period of follow-up is currently unknown for studies on adverse effects of MTX. In this study, postoperative complications were evaluated within 1 year after surgery on the basis of the previous studies by Grennan et al.[8] It is also uncertain when flare-up of RA should be evaluated after discontinuance of MTX before surgery. In the paper by Kremer et al.,[10] significant worsening of symptoms is found within 4 weeks after discontinuance of MTX (mean: 14 mg, range: 10–20 mg/week) in RA patients who have taken the DMARDs for at least 3 years. Therefore, disease flare-up was evaluated within 4 weeks after surgery in this study.

There is a concern that NSAIDs may decrease the clearance of MTX by the kidneys, leading to an increase in potential side effects of MTX. Our present study, however, revealed no association of NSAIDs with the risk of postoperative complications, possibly because Japanese patients with RA take relatively low doses of MTX.

Overall, we recommend the perioperative use of MTX, especially for the patients with high RA activity who receive high doses of DMARDs. Discontinuance of MTX could cause flare-up of RA, resulting in delayed rehabilitation and mobilization after elective orthopedic surgeries.

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