



## Methotrexate and post operative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery – A ten year follow-up

Ramankutty SREEKUMAR, Julie GRAY, Peter KAY, David Michael GRENNAN

*From Wrightington Hospital Wigan, United Kingdom*

In the 1990's there were concerns that methotrexate might increase the risk of post operative complications following elective orthopaedic surgery ; as a result many Units initiated policies to discontinue methotrexate prior to elective orthopaedic surgery. In 2001 we carried out a controlled study of complications after elective surgery in rheumatoid arthritis (RA) patients who either continued or discontinued methotrexate prior to surgery. In this study we showed that continuation of methotrexate therapy prior to orthopaedic surgery did not increase the risk of infection or surgical complication occurring in patients with RA within one year of surgery. The limitation of this study was that complications later than one year were not studied.

Sixty-five patients have been followed up. Thirty-one were fully assessed in clinic and 34 underwent a structured telephone interview.

There were no incidences of deep bone infection in any patient group so that there is no evidence that continued methotrexate therapy in the perioperative period increases the risk of late deep infections.

We adhere to our original advice that in the absence of renal failure or sepsis, methotrexate therapy should not be stopped before elective orthopaedic surgery in patients with RA whose disease is controlled by the drug before surgery.

**Keywords :** methotrexate ; joint replacement surgery ; rheumatoid arthritis ; infection.

## INTRODUCTION

Rheumatoid arthritis is a disabling inflammatory condition which is treated with methotrexate, though there are many new drugs currently used in addition or in place of methotrexate (1). There have been studies indicating that continuation of methotrexate during the intraoperative phase causes complications including infection (1). There were additional prospective and retrospective studies confirming this finding (2,4,6,7). These studies led to the practice of stopping methotrexate 4 weeks prior to surgery and restarting after surgery. Unfortunately, this led to aggravation of the rheumatoid symptoms after surgery.

In a previous study (3) we showed that continuation of methotrexate therapy prior to orthopaedic surgery did not increase the risk of infection or surgical complication occurring in patients with RA

- 
- Ramankutty Sreekumar, FRCS, Orthopaedic Surgeon.
  - Julie Gray, Clinical Trials.
  - Peter Kay, Consultant Orthopaedic Surgeon.
  - David M. Grennan, Consultant Rheumatologist.

Correspondence : Ramankutty Sreekumar, Wrightington Hospital, Hall Lane, Appley Bridge, Wigan WN6 9EP.

E-mail : r.sreekumar@doctors.org.uk

© 2011, Acta Orthopædica Belgica.

Table I. — Patients studied (n = 388)

Subjects	Group A (n = 88)*	Group B (n = 72) <sup>o</sup>	Group C (n = 228)*
Died	17	20	79
Contacted by Phone	9	5	20
Refused	1	7	6
Reviewed in Clinic	14	3	14
Lost to Follow-up	47	37	109

\* Numbers refer to those in the original study (3).

within one year of surgery. Patients were divided in three groups (Table I).

Group A : patients with RA who were receiving methotrexate for at least six weeks before surgery and in whom methotrexate treatment was not discontinued. Group B : patients with RA who were receiving methotrexate matched with Group A for type of surgery and in whom methotrexate treatment was stopped two weeks before surgery and restarted two weeks after surgery. Group C : patients with RA who underwent elective orthopaedic surgery during the study period and who had not received methotrexate treatment.

We noted and analyzed the influence of sex, rheumatoid disease duration, baseline disease activity as measured by the articular index, Health Assessment Questionnaire score, the influence of other drug treatments including penicillamine, corticosteroids and non steroidal inflammatory drugs, the presence of concurrent diseases such as diabetes, hypertension, osteoporosis, vasculitis, bronchiectasis, Felty's syndrome, asthma, ischaemic heart disease, and diverticulitis. Information about these was obtained either from the patients case notes or by interviewing the patient before surgery. The patients in the 3 groups had undertaken replacement of the major joints or the metacarpophalangeal joints or fusion of the joints of the hand and feet (Table III). The details of the surgical procedures have been outlined in the earlier paper. The limitation of this study was that complications later than one year were not studied. We have now been able to study complications occurring between one and ten years post surgery to exclude the possibility that

continued methotrexate therapy in RA patients might increase the risk of late complications following elective orthopaedic surgery.

## METHOD

### Subjects

Approval was obtained from the regional Ethics Committee to carry out this study. We reviewed the original database and excluded the patients who had died since the time of surgery. We wrote to all surviving patients to obtain their approval to participate in this ten year follow-up study. We were unable to contact 193 patients (see Table I and II), 14 patients did not wish to take part in the follow-up study and 31 agreed to be reviewed in clinic by RS and 34 patients took part in a structured telephone interview with the first author (RS). All patients who were reviewed in clinic had a history, clinical examination and a radiograph where clinically indicated. RS was unaware at the time of assessment which clinical group each individual patient belonged to.

### Surgical Complications

Surgical complications were defined as any condition requiring revision surgery other than infection. By clinical infection we mean any infection around the operation site or deep bone infection. As in the original study patients were considered in three groups.

### Statistics

We have analysed the age, gender and the proportion of patients undergoing upper limb versus lower limb surgery in patients followed up as compared to those

Table II. — Age and gender of patients followed-up versus drop-outs/deaths

	Group A Reviewed/ Contacted (n = 23)	Group A Drop-outs/ Deaths (n = 65)	Group B Reviewed/ Contacted (n = 8)	Group B Drop-outs/ Deaths (n = 64)	Group C Reviewed/ Contacted (n = 34)	Group C Drop-outs/ Deaths (n = 194)
Female (n)	19	53	7	49	26	163
Mean Age (years)	56	59	53	59	57	61
Range	(39-73)	(16-83)	(39-64)	(29-82)	(38-57)	(28-83)
Male (n)	4	12	1	15	7	32
Mean Age (years)	53*	65*	71*	64	58	62
Range	(48-55)	(56-72)	(40-79)	(38-71)	(42-82)	

\* Age at time of Surgery.

None of these differences between those followed up and dropouts/deaths were statistically significant (Fisher).

Table III. — Proportion of patients undergoing upper limb surgery versus lower limb surgery in patients followed up versus patients not followed up

	Group A Reviewed/ Contacted (n = 23)		Group A Drop-outs/ /Deaths (n = 65)		Group B Reviewed/ Contacted (n = 8)		Group B Drop-outs/ /Deaths (n = 64)		Group C Reviewed/ Contacted (n = 34)		Group C Drop-outs/ /Deaths (n = 194)	
	No	%	No	%	No	%	No	%	No	%	No	%
Upper Limb	15	65	31	48	5	63	28	48	16	47	107	55
Lower Limb	8	35	34	52	3	38	36	56	17	50	88	45

None of these differences between those followed up and dropouts/deaths were statistically significant.

patients who were not followed up to exclude statistical bias in those dropping out. It was not possible to statistically analyse the residual population of patients at 10 years follow-up as the numbers were not adequate.

## RESULTS

There were no incidences of deep bone infection in the patients followed up between one and ten years post surgery (Table V). There were three patients with aseptic loosening of the prosthesis, two in Group A and one in Group C (Table IV). Revision surgery was performed in one patient in Group A (where a failed wrist replacement was converted to a fusion) and the patient in Group C (a cystic lesion adjacent to the tibial component of the

ankle prosthesis was bone grafted). The other patient in Group A has not had a revision, has a loose ankle prosthesis and is mobilising with a scooter due to other co morbidities.

Of the patients who had died, there was no evidence of sepsis having contributed to their death.

## DISCUSSION

The main aim of this study was to establish whether continuing methotrexate perioperatively increased the risk of late post operative complications or deep infections in patients with RA who underwent elective orthopaedic surgery. Clearly in these subjects the risk of late deep infections was

Table IV. — Radiological analysis 10 years post surgery

	Group A (n = 23)		Group B (n = 8)		Group C (n = 34)	
	No	%	No	%	No	%
Lysis	5	22	1	13	4	12
Loose Components	2	9	0	0	1	3

Table V. — Subjects who developed complications/infections between 1 and 10 years post surgery

	Group A (n = 23)		Group B (n = 8)		Group C (n = 34)	
	No	%	No	%	No	%
Clinical Infection	0	0	0	0	0	0
Surgical Complications	2	9	0	0	1	3

not increased as there were no incidences of late deep infections in any patient group. There was one subject who required revision surgery in the subjects who had continued methotrexate therapy (Group A) but clinically there was no evidence of sepsis in this patient. On the other hand x-ray analysis has show that 22% of patients who continued methotrexate versus 13% patients who discontinued methotrexate had asymptomatic lysis on radiographs. There was no evidence of infection in these patients and these findings are most unlikely to be drug related.

It could be argued that as 193 patients out of the original group of 388 have been lost to follow-up, many complications may have occurred in this group. However as far as we can see the group followed up were representative of the original group in terms of age, gender and type of surgery.

In conclusion, we adhere to our original advice that in the absence of renal failure or sepsis, methotrexate therapy should not be stopped before elective orthopaedic surgery in patients with rheumatoid arthritis whose disease is controlled by the drug before surgery.

## REFERENCES

- Bridges S, Lopez Mendez A, Han K, Tracy F, Alarson G.** Should Methotrexate be discontinued before elective orthopaedic surgery in patients with rheumatoid arthritis? *J Rheumatol* 1991 ; 18 : 984-988.
- Carpenter M, West S, Jones D.** Post operative joint infections in rheumatoid arthritis patients on methotrexate therapy. *Orthopedics* 1996 ; 19 : 207-210.
- Grennan DM, Gray EJ, Loudon J, Fear S.** Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. *Ann Rheum Dis* 2001 ; 60 : 214-217.
- Kasden M, June L.** Postoperative results of rheumatoid arthritis patients on methotrexate at the time of reconstructive surgery of the hand. *Orthopedics* 1993 ; 16 : 1233-1235.
- Kremer JF.** The changing face of therapy for rheumatoid arthritis rheumatic disease. *Rheum Dis Clin North Am* 1995 ; 21 : 845-860.
- Perhala R, Wilke W, Clough J, Segal A.** Local infectious complications following large joint replacements in rheumatoid arthritis patients treated with methotrexate versus those not treated with methotrexate. *Arthritis Rheum* 1991 ; 34 : 146-152.
- Sany J, Ananya J, Canovas F et al.** Influence of methotrexate and the frequency of postoperative infections/complications in patients with rheumatoid arthritis. *J Rheumatol* 1993 ; 20 : 1129-1132.