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H. Nakamura · M. Nagashima · S. Ishigami · K. Wauke
S. Yoshino

The anti-rheumatic effect of multiple synovectomy in patients with refractory rheumatoid arthritis

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Abstract We assessed the anti-rheumatic effects of radical multiple synovectomy (RaMS) in patients with rheumatoid arthritis (RA) who did not respond to intensive medical treatment. The selection of patients into three groups, A, B or C, was randomised. Patients assigned to group A ($n=28$) continued the prescribed pre-operative medication and had RaMS. Patients assigned to group B ($n=20$) were started on a combination therapy with disease-modifying anti-rheumatic drugs (DMARDs) after radical multiple synovectomy. Nineteen RA patients who were started on the same combination therapy as group B but who did not undergo surgery served as controls (group C). The clinical and radiographic findings were assessed for at least 3 years after surgery. Patients in the surgically treated groups (groups A and B) showed a significant reduction in the number of swollen and painful joints and in their ESR and serum CRP levels, and this effect was maintained for at least 3 years. More than 40% of the patients remained in clinical remission during the observation period. The surgical outcome seemed to be superior to that of the controls and did not differ between group A and group B. Articular destruction (assessed by the carpal height ratio) did not progress in the patients who were in clinical remission.

Résumé Nous avons étudié les effets anti-rhumatoïde de la synovectomie complète multiple dans trois groupes de patients atteints d'arthrite rhumatoïde réfractaire au traitement médical. La sélection des patients en trois groupes a été faite au hasard. Les patients du groupe A ($n=28$) ont continué le traitement pré-opératoire prescrit; ceux du groupe B ($n=20$) ont commencé, après l'intervention un traitement par médicaments anti-rhumatismaux. Enfin 19 patients qui ont commencé la même combinaison thérapeutique que le groupe B mais sans in-

tervention chirurgicale ont servi de groupe de contrôle. Les patients ont été suivis au moins 3 ans après le traitement chirurgical. Les patients traités par synovectomie ont montré une réduction du nombre d'épanchement, de douleurs articulaires ainsi qu'une diminution de la vitesse de sédimentation et du niveau de la CRP ceci s'étant maintenu pour au moins 3 ans. Plus de 40% des patients sont restés en rémission clinique durant la période d'observation. Les destructions articulaires mesurées par la hauteur du carpe n'ont pas progressé pendant la période de rémission.

Introduction

The inflamed synovium in rheumatoid arthritis (RA) produces many cytokines including interleukin-1 (IL-1), IL-6, tumour necrosis factor α (TNF α) and proteolytic enzymes [1, 3, 4, 9] which promote articular destruction. It was thought likely that surgical removal of the synovial tissue would reduce the total amount of cytokines and enzymes produced, thus providing an anti-rheumatic effect. In order to reduce the disease activity we developed a method of radical multiple synovectomy (RaMS) for patients with refractory RA, and this involves thorough excision of the pathological synovial tissue of as many swollen joints in the body as possible [11, 14]. In the present study we assessed the anti-rheumatic effect of this surgery.

Patients and methods

A total of 48 patients who fulfilled the diagnostic criteria for RA [12] and were unresponsive to intensive anti-rheumatic medical treatment underwent RaMS, and all gave informed consent for the surgery. Of the 48 patients who underwent surgery, 28 were randomly assigned to group A and continued to take the prescribed pre-operative anti-rheumatic medication even after the operation, and 20 who were assigned to group B were started on combination therapy with DMARDs post-operatively. This combination therapy consisted of a combination of three or four DMARDs, including sulfasalazine and/or bucillamine along with corticosteroids

H. Nakamura · M. Nagashima · S. Ishigami · K. Wauke
S. Yoshino (✉)

Department of Joint Disease and Rheumatism,
Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku,
Tokyo 113-8603, Japan
Tel: +81-3-5814-6441, Fax: +81-3-3822-2170

Table 1 Patients' profiles (MTX methotrexate, DMARD disease-modifying anti-rheumatic drug)

	Group A (n=28)	Group B (n=20)	Group C (n=19)
Surgical procedure	RaMS	RaMS	None
Post-operative treatment	Constant ^a	Combination ^b	Combination
Pre-operative medication			
Corticosteroids	26 (92.9%)	18 (90.0%)	17 (89.5%)
MTX	22 (78.6%)	13 (65.0%)	8 (42.1%)
DMARDs	18 (64.3%)	12 (60.0%)	9 (47.4%)
Combination	13 (46.4%)	7 (35.0%)	1 (5.3%)
Age at initial examination (yrs)	56.8 (44–73)	58.3 (42–76)	54.2 (22–73)
Disease duration (yrs)	14.6 (2–30)	13.5 (3–34)	9.9 (1–26)

^a Post-operative medication identical to pre-operative medicine

^b Corticosteroids + MTX + DMARDs

Table 2 Number of surgically treated joints

Joint	Number
Proximal interphalangeal	56
Metacarpo-phalangeal	229
Wrist	70
Elbow	62
Knee	52
Ankle	67
Shoulder and metatarso-phalangeal	21

and methotrexate (MTX). Group C consisted of 19 RA patients who were also given the same combination therapy but did not undergo synovectomy (Table 1).

Surgical procedure. Open synovectomy was performed on as many clinically swollen joints as possible, and this included the proximal interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, knee, ankle and metatarsophalangeal joints. As much synovial tissue as possible was removed by excision using a conventional technique [11, 14]. Synovectomy was performed in all the joints at the same time except in cases where the procedure was indicated for both upper limbs. In these exceptions secondary surgery on the other upper limb was performed following an interval of at least 3 weeks. After surgery we encouraged patients to move their joints and they were allowed to walk as soon as the drainage had been removed, usually the second day after operation. Patients underwent synovectomy on an average of 11.8 joints (Table 2).

Statistical analysis. Comparisons of post-operative findings against the baseline values were analysed using the Wilcoxon signed-ranks test. Differences in the clinical and laboratory values between groups were randomised using the Mann-Whitney *U*-test or Fisher's exact probability test. Significance was estimated at the $P < 0.05$ level.

Results

The number of swollen and painful joints was recorded, and the erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) levels and serum rheumatoid factor (RF) titers were measured prior to and at 3, 6, 12, 18, 24 and 36 months after operation. The percentage of patients in remission was assessed according to the ACR criteria for clinical remission [12] at each examination. Finally, articular destruction was assessed on a radiograph of the hands using Larsen's damage score (DS) [6] and the carpal height ratio (CHR: ratio of carpal height

Table 3 Baseline clinical and laboratory findings

	Group A	Group B	Group C
Swollen joints	14.0 ^a	15.9 ^a	12.9 ^a
Painful joints	4.5 ^a	4.7 ^a	3.7 ^a
ESR (mm/h)	59.2±34.4 ^b	62.3±20.3 ^b	71.9±23.0 ^b
CRP (mg/dl)	4.0±3.9 ^b	4.0±2.7 ^b	4.0±2.7 ^b
RF (mg/ml)	202±336 ^b	358±467 ^b	175±277 ^b

^a Average number of joints

^b Values are means ± SD

to length of the third metacarpal) [15] before operation and 3 years post-operation.

Baseline clinical and laboratory findings

No significant differences were found in respect to age, number of painful joints, ESR, serum CRP levels and RF titers among the three groups prior to surgery. The disease duration was shorter and the number of painful joints were fewer in group C patients (Table 3).

Surgical results

Three months after operation the number of swollen and painful joints was significantly decreased and remained so for at least 3 years in the patients who underwent surgery. In group B a significantly decreased number of swollen and painful joints was seen at 12 and 36 months after operation (Fig. 1a,b). The ESR and serum CRP levels improved shortly after the operation in groups A and B, while improvement was delayed in group C (Fig. 1c,d).

Remission rate

Remission was noted at 3 months after surgery in 75% of group A patients and 60% of group B patients, but there was no improvement in group C (0%). During the course of the study the remission rate in groups A and B was over 40% compared to 0% in group C and did not differ significantly between groups A and B (Fig. 2).

Fig. 1a–d Surgical results of RaMS in group A (●) and B (○) in comparison with group C (□). **a** Mean number of swollen joints. **b** Mean number of painful joints. **c** Mean ESR rate. **d** Mean serum C-reactive protein level. Comparisons against baseline values were made by Wilcoxon signed-ranks test. * $P < 0.05$

Fig. 2 Percentage of patients in group A (●), B (○) and C (□) who fulfilled the ACR criteria for clinical remission. Comparisons were made by Fisher's exact probability test. * $P < 0.05$

Radiographic findings

Articular destruction progressed in all groups (assessed by the DS and CHR). However, those patients who had undergone synovectomy and who fulfilled the criteria of remission on more than three follow-up visits showed little progression of the CHR (Fig. 3).

Discussion

In the past synovectomy has been reported to lead to reduction of joint pain, joint swelling and articular destruction, particularly in the early stages of rheumatoid arthritis [2, 4, 5]. Despite these favourable reports, however, synovectomy has not been performed in recent years as a result of the outcome of a controlled multicentre study conducted in the United States [8]. This showed that synovectomy did not prevent recurrences or produce radiological improvement which could last 5 years. However, this American study was intended to demonstrate the surgical outcome of synovectomy for a single joint and consequently did not deal with the general anti-rheumatic effects of this management. We thought that complete excision of the inflamed synovium of as many joints in the body as possible could cause remission and prevent articular destruction and RaMS in a procedure in which pathological synovial tissue is excised as thoroughly as possible following intensive medical treatment.

In our study, RaMS was performed on patients in whom the disease was considered to be severe and who did not respond to intensive conventional medical treatment including MTX, DMARDs or a combination of both. In regard to combination therapy associated with surgical treatment a combination of MTX, azathioprine and anti-malarial drugs has been reported to induce remission in a high proportion of cases [7]. In addition, biological agents such as the TNF α antibody [13] and TNF fusion protein [10] are being developed for the treatment of refractory RA. However, we must pay attention to the adverse effects of such treatments in severe disease.

Fig. 3a–c Articular destruction evaluated in radiographs of the hands in group A (●), B (○) and C (□). **a** Damage score by Larsen. **b** Carpal height ratio. **c** No progression of carpal height ratio was observed in surgical patients who showed remission at three post-operative visits. Comparisons against baseline values were made by Wilcoxon signed-ranks test. * $P < 0.05$

On the other hand, excision of the synovium has been demonstrated to be a safe technique with few serious complications and in the present series we encountered no serious adverse effects due to the surgery.

To determine the influence of post-operative medication on the efficacy of RaMS, we compared the results of RaMS with those of combination therapy. We found, in respect to all variables, that surgery produced superior results to combination therapy without surgery. Moreover, there was no difference in the clinical outcome between surgery plus post-operative combination therapy (group B) and surgery plus the same medication as prescribed pre-operatively (group A). Thus RaMS alone appears to exert anti-rheumatic effects.

RaMS exerted a positive effect on pain and swelling shortly after surgery and this effect lasted for at least 3 years. In addition, more than a third of patients remained in remission for at least 3 years. Although articular destruction as assessed by the DS and CHR proceeded in all groups, the CHR showed no significant progression in patients who showed a good post-operative course following RaMS. This suggests that RaMS may offer protection against articular destruction. Thus this procedure may provide benefit for patients who have severe RA but who do not respond to conventional medical treatment.

Based on the present results RaMS demonstrates anti-rheumatic effects, and may delay the need for other complex surgery such as total joint arthroplasty. This latter procedure is highly invasive and expensive and some patients do not respond favourably, and therefore it should be reserved for patients with severe disease who show little response to conventional medical treatment and multiple synovectomy.

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