■ KNEE

Inflammation related to synovectomy during total knee replacement in patients with primary osteoarthritis

A PROSPECTIVE, RANDOMISED STUDY

A. Tanavalee,
S. Honsawek,
T. Rojpornpradit,
M. Sakdinakiattikoon,
S. Ngarmukos

From the Department of Orthopaedics, Chulalongkorn University, Bangkok, Thailand

We compared inflammation in the knee after total knee replacement (TKR) for primary osteoarthritis between two groups of patients undergoing joint replacement with and without synovectomy. A total of 67 patients who underwent unilateral TKR were randomly divided into group I, TKR without synovectomy, and group II, TKR with synovectomy. Clinical outcomes, serial serum inflammatory markers (including interleukin-6 (IL-6), CRP and ESR) and the difference in temperature of the skin of the knee, compared with the contralateral side, were sequentially evaluated until 26 weeks after surgery.

Pre-operatively, there were no statistically different clinical parameters between groups I and II. At the 26-week follow-up, both groups had a similarly significantly improved American Knee Society clinical score ($p < 0.001$) and functional score ($p < 0.001$) with no differences between the groups. Similar changes in serial inflammatory markers were found in both groups, including mean peak levels of IL-6 (189 pg/ml (SD 53.4) *versus* 201 pg/ml (SD 49.4) for groups I and II, respectively) and CRP (91 mg/L (SD 24.1) *versus* 88 mg/L (SD 23.4), respectively) on the first post-operative day, returning to pre-operative values at two and six weeks, respectively. The mean peak level of ESR for the respective two groups was 46 mm/hr *versus* 48 mm/hr at two weeks, which had still not returned to its pre-operative mean value at 26 weeks. The elevation in the skin temperature appeared to mirror the peak elevation of the ESR, with a range of 2.5° C to 4.5° C with some reduction at 26 weeks but still exceeding the pre-operative value.

We concluded that synovectomy at the time of TKR does not provide any benefit to the clinical outcome or shorten the duration of the inflammatory response after surgery.

■ A. Tanavalee, MD, Associate Professor
■ S. Ngarmukos, MD, Instructor
Department of Orthopaedics
■ S. Honsawek, MD, PhD, Associate Professor
Department of Biochemistry
Chulalongkorn University, 1873 Rama IV Road, Pathumwan, Bangkok 10330, Thailand.

■ T. Rojpornpradit, MD, Orthopaedic Surgeon
Department of Orthopaedic Surgery
Siridhorn Hospital, 20 Soi Onnuch 90, Pravet, Bangkok 10250, Thailand.

■ M. Sakdinakiattikoon, MD, Orthopaedic Surgeon
Department of Orthopaedic Surgery
Bangkok Metropolitan Administration General Hospital, 514 Luang Road, Pomprab Satrupai, Bangkok 10100, Thailand.

Correspondence should be sent to Professor A. Tanavalee; e-mail: areetana@hotmail.com

doi:10.1302/0301-620X.93B8.26719 $2.00

J Bone Joint Surg [Br] 2011;93-B:1065-70.
Received 14 January 2011; Accepted after revision 14 May 2011

Synovial proliferation is a common intra-operative finding in patients with osteoarthritis or other inflammatory conditions of the knee.[1-3] Surgical synovectomy, excising the inflamed or proliferated synovial membrane, reduces pain and improves joint function[1-4] and is beneficial for patients with rheumatoid arthritis and other inflammatory conditions.[5,6]

Although many inflammatory cytokines have been isolated from the knee and the blood in patients with moderate to severe primary osteoarthritis,[7] the benefit of synovectomy as a sole procedure in primary osteoarthritis remains unclear. Most studies have reported favourable results following synovectomy combined with other specific surgical procedures.[2-4]

Synovectomy undertaken during total knee replacement (TKR) depends on the surgeon's preference. Krackow[8] recommended that as little synovium as possible should be removed and Yasgur, Scuderi and Insall[9] recommended that only sufficient synovium should be excised to ensure adequate visualisation. Synovitis has been reported as one of several contributing factors in unsatisfactory results after TKR.[10] This raises the question as to whether intra-operative synovectomy during TKR would be advantageous in decreasing post-operative inflammation of the knee.

The objective of this study was to compare the effect of synovectomy during TKR on inflammation of the knee in patients with primary osteoarthritis of the knee using clinical outcomes, serial monitoring of serum inflammatory markers and the skin temperature of the knee. We hypothesised that the post-operative inflammation would be no different between patients who undergo TKR with or without intra-operative excision of synovial membrane.

Patients and Methods

This study was approved by our Institutional Review Board and conducted in accordance with the guidelines of the Declaration of

Table I. Patients' characteristics for group I (total knee replacement (TKR) without synovectomy) and group II (TKR with synovectomy) with the American Knee Society scores (AKSS) for clinical and functional outcome

Parameters	Study group	Group I	Group II	p-value*
Number of knees	67	33	34	
Male:female	13:54	9:24	4:30	0.132†
Mean age (range) (yrs)	70.0 (54 to 86)	70.1 (54 to 86)	69.8 (54 to 85)	0.821
Mean BMI‡ (range) (kg/m^2)	27.7 (19.9 to 37.1)	28.2 (20.2 to 35.9)	27.2 (19.9 to 37.1)	0.254
Mean AKSS clinical score (range)				
Pre-operative	50.2 (39 to 57)	50.2 (39 to 57)	50.2 (40 to 56)	1.0
26-week post-operative	90.1 (86 to 96)	90.4 (88 to 96)	90.0 (86 to 95)	0.747
Mean AKSS function score (range)				
Pre-operative	41.4 (35 to 50)	40.8 (35 to 50)	42.0 (37 to 49)	0.372
26-week post-operative	82.6 (75 to 90)	81.9 (75 to 89)	83.3 (77 to 90)	0.255

* Student's *t*-test, unless otherwise stated
† chi-squared test
‡ BMI, body mass index

Helsinki.[11] Written informed consent was obtained from the patients prior to their participation. As there has been no similar report in the literature, the sample size was designed according to the standardised effect size of 0.7, using Student's *t*-test to compare means of continuous variables, a statistical power of 0.8, and a p-value of 0.05. Thus 32 patients (knees) were required in each group.

Between September 2007 and December 2008, 67 patients (54 women and 13 men) with late-stage primary osteoarthritis of the knee according to the American College of Rheumatology (ACR) criteria[12] with grade IV radiological changes according to the classification of Kellgren and Lawrence[13] were scheduled for TKR and evaluated. The mean age of the 67 patients (67 knees) was 70.0 years (54 to 86) and the mean BMI was 27.7 kg/m^2 (19.9 to 37.1). Group I comprised 24 women and nine men and group II consisted of 30 women and four men (Table I). Exclusion criteria included patients younger than 50 years old, those with inflammatory arthritis, arthritis secondary to a systemic or autoimmune disorder, a pre-operative ESR > 40 mm/hr, history of cancer or chronic illness, and symptomatic arthritis of the other knee. Following the surgery, all patients received the same rehabilitation protocol with follow-up visits scheduled at two, six, 14 and 26 weeks after surgery. Blood levels of interleukin-6 (IL-6), ESR and CRP, as well as skin temperature of both knees, were evaluated pre-operatively and at the follow-up visits.

Surgical technique and post-operative care. All operations were performed by a single surgeon (AT) using a mini-midvastus approach[14] with a tourniquet pressure of 300 mmHg. The routine anaesthetic involved a spinal block, proceeding to a general anaesthesic if this was ineffective. A 4 cm dissection along the fibres of vastus medialis obliquus was made to gain a complete visualisation of the whole anterodistal femur when the knee was flexed to 90°. All visible osteophytes were removed, and both cruciate ligaments were resected.

Randomisation was performed using a computer random generator. In group I patients (TKR without synovectomy, n = 33), all synovial membrane was retained. However, the synovial membrane at the anterior cortex of the distal femur was subperiosteally undermined in order to seat the anterior flange of the femoral component. In group II patients (TKR with synovectomy, n = 34), a full thickness layer of the synovial membrane lining the knee joint, and that covering the anterior cortex of the distal femur and the patellar tendon (about 4 cm^2 to 6 cm^2) were excised. Subsequent visible points of haemorrhage were treated with electrocautery.

The bone resection was made in the sequence of distal femur, proximal tibia, anterior femur, posterior femur, chamfer, and then patella. The patella was resurfaced in all patients and all the components were cemented. The NexGen posterior stabilised knee system (NexGen-LPS; Zimmer, Warsaw, Indiana) was used in all knees.

The tourniquet was not deflated before wound closure and application of the dressing. A vacuum drain was used and removed at 18 to 22 hours after operation. Post-operative pain management did not involve an intra-articular injection; a single multimodal pain control protocol was used, including combined selective cyclooxygenase-2 (COX-2) inhibitors (three doses of 40 mg parecoxib starting at the end of surgery, and then ten to 14 days of 90 mg etoricoxib), two days of 500 mg paracetamol every six hours, and 1 mg to 2 mg intravenous morphine every three hours for any breakthrough pain during the first 36 hours. For those who had general anaesthesia, a similar protocol was used with the additional availability of intravenous patient control analgesia (PCA; morphine). A total of three patients in each group had general anaesthesia.

Evaluation of knee inflammation. Blood samples were collected the day before surgery and at each follow-up visit. All samples were centrifuged to remove cells and debris, and stored at -80°C until analysis. The CRP was measured using the latex particle enhanced nephelometric immune assay on the BN ProSpec analyser (Dade Behring, Marburg, Germany). The ESR was determined using the Westergren method.[15] The IL-6 was measured using

commercially available human IL-6 enzyme-linked immunosorbent assay (ELISA) MAX sets (Biolegend, San Diego, California) according to the manufacturer's instructions. Briefly, 96-well micro-titre plates were pre-coated with monoclonal antibody supplied in the kit, and a blocking solution was added to eliminate nonspecific antigen binding. After washing, the wells were incubated with either serum or known concentration standards of recombinant human IL-6 at room temperature. After plate washing, a biotin-labelled detection antibody was added. Following incubation and washing, an avidin-horseradish peroxidase enzyme and colour substrate was applied for the detection of binding. Finally, the reaction was stopped with the stop solution, and then light absorbance was measured at a wavelength of 450 nm using an automated microplate reader. Recombinant human IL-6 was used to develop a standard curve.

Skin temperature was measured on the same days as the blood tests and at the same time of the day between 11 am and 12 noon at a standard environmental temperature of 25°C, using a single digital infrared surface thermometer at four different locations on the anterior aspect of the knee (superomedial, superolateral, inferomedial, and inferolateral border of the patella). The mean temperature for the four locations was taken as the final temperature. A similar measurement was also carried out on the contralateral knee as a control for individual patients. The difference in temperature between the operated and contralateral side was reported.

Clinical assessment. Clinical outcomes, including the American Knee Society score (AKSS; clinical and function),[16] range of movement, pain score (part of the clinical AKSS, ranging from 50 (no pain) to 0 (severe pain)), and knee surface temperature were evaluated pre-operatively and were sequentially evaluated post-operatively until 26 weeks by two independent observers (TR and MS). The mean values of the parameters measured from both observers were used.

Statistical analysis. Statistical analysis was performed using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego, California). Descriptive statistics were expressed by mean and SD. Comparisons between groups were undertaken using unpaired Student's *t*-tests. The chi-squared test was used for qualitative comparative parameters. A p-value of < 0.05 was considered statistically significant.

Results

There were no statistical differences in patients, demographic data or the mean pre-operative AKSS (clinical and functional) between the groups (Table I).

At 26-week follow-up, both groups had significantly improved mean clinical and functional AKS scores (*t*-test, both $p < 0.001$) with no differences between groups (Table II). There were no infections and no patient required re-operation for any reason.

Table II. Comparison of changes in the American Knee Society scores (AKSS: clinical and functional) within the two groups

	Pre-operative		26-week post-operative		
Group and parameters	**Mean**	**SD**	**Mean**	**SD**	**p-value***
Group I (33 knees)					
AKSS (clinical)	50.2	6.9	90.4	7.1	< 0.001
AKSS (function)	40.8	5.9	81.9	6.0	
Group II (34 knees)					
AKSS (clinical)	50.2	6.7	90.0	6.8	< 0.001
AKSS (function)	42.0	5.2	83.3	5.0	

* Student's *t*-test

Pre-operatively, there were no statistical differences in the measurements of inflammation between groups I and II including the mean IL-6 levels (59.0 pg/ml (SD 16.5) *vs* 62.0 pg/ml (SD 19.8), respectively), mean CRP values (9.0 mg/L (SD 2.2) *vs* 11.0 mg/L (SD 2.4), respectively), mean ESR (24.0 mm/hr (SD 19.0) *vs* 23 mm/hr (SD 15.0), respectively), and mean skin temperature (33.3°C (SD 0.4) *vs* 33.6°C (SD 0.5), respectively). Serial assessment of the inflammatory markers of groups 1 and 2 revealed peak elevations of the mean IL-6 level (189.0 pg/ml (SD 53.4) *vs* 201.0 pg/ml (SD 49.4), respectively) and CRP (91.0 mg/L (SD 24.1) *vs* 88.0 mg/L (SD 23.4), respectively) on the first post-operative day (Figs 1 and 2). These parameters fell to pre-operative values at two weeks and six weeks, respectively. Similarly, both groups had increased level of ESR to a mean peak (48.0 mm/hr (SD 28.0) *vs* 49.0 mm/hr (SD 27.0), respectively) at two weeks. The elevated ESR values persisted to six weeks with slight decreases at 14 weeks and 26 weeks post-operatively (Fig. 3). Both groups had similar elevated skin temperature to a peak corresponding to the level of ESR at the range of 2.5 to 4.5°C. At the 26-week follow-up, both groups still had a mean of 1.0°C elevated temperature (Fig. 4).

Discussion

Although the ESR and CRP are commonly used in orthopaedics as routine screening tests for the diagnosis of potential infection, the rise in ESR demonstrates a nonspecific haematological response to inflammation. Similarly, the CRP represents acute phase protein which is produced by the liver in response to non-specific inflammatory conditions.[17,18] The IL-6, which is principally responsible for activating the hepatic synthesis of CRP, is produced substantially by monocytes and macrophages after antigen activation, even though other cells may also synthesise it.[7]

Although the three inflammatory markers (IL-6, ESR and CRP) are non-specific for the evaluation of inflammation of a specific organ, serial monitoring of these markers in combination with monitoring of skin temperature around the knee in well selected arthritic patients provided a rational evaluation of inflammation. In the present study, we adhered to strict selection criteria to avoid confounding

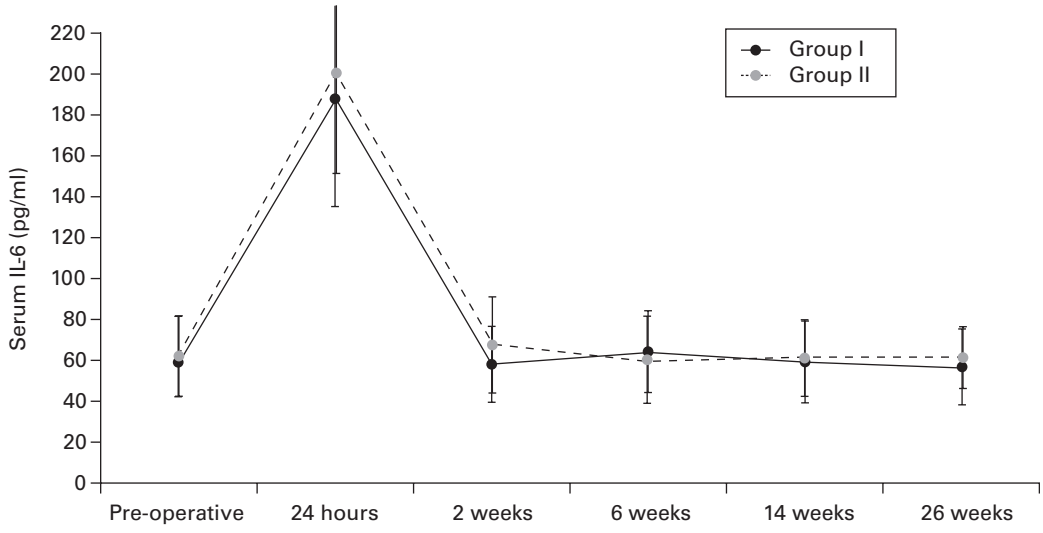

Fig. 1

Plot graph showing the mean serum IL-6 levels between patients who underwent total knee replacement (TKR) without synovectomy (group I) or with synovectomy (group II) from pre-operative period to 26-week follow-up (error bars represent SDs).

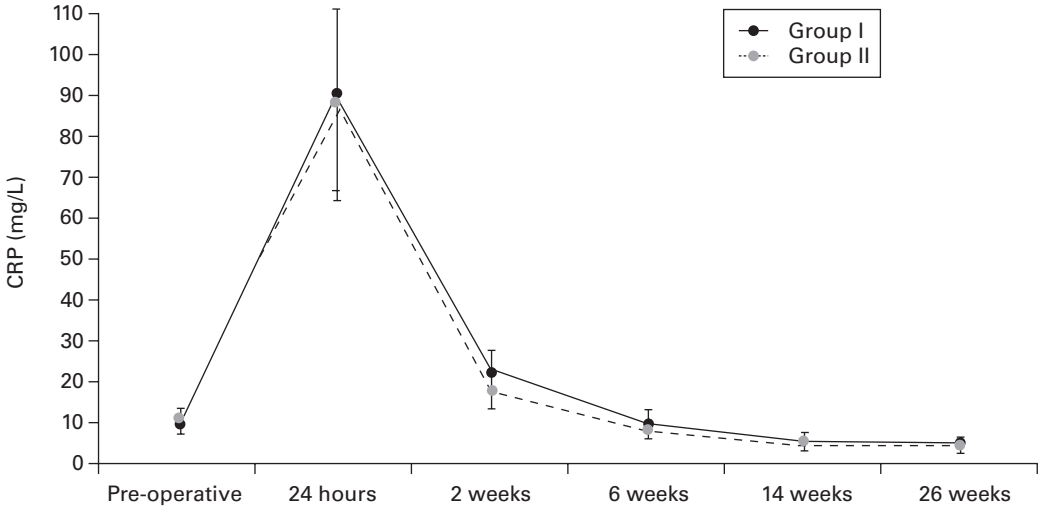

Fig. 2

Plot graph showing the mean CRP levels of patients who underwent total knee replacement without synovectomy (group I) or with synovectomy (group II) from pre-operative period to 26-week follow-up (error bars represent SDs).

from other sources of inflammation. In addition, we evaluated the inflammation around the knee for 26 weeks in order to avoid the possible effect of an increasing incidence of painful contralateral knee arthritis which we have reported previously.[19]

According to our findings, the elevation and changes of serum IL-6, ESR and CRP in both groups were not statistically different. Additionally, the results for the parameters investigated were in agreement with previous studies of inflammatory markers after joint replacement, in terms of time to peak elevation, decreasing to normal levels and the extent of the increases.[20,21] The present study also included monitoring of skin temperature of the operated knee, which rose significantly after the surgery and gradually decreased by 26 weeks post-operatively, with no difference between the groups. The change of skin temperature seemed to mirror the level of the inflammatory markers, especially the ESR, which was similar to the study of Mehra et al.[22] Concerning the different skin temperature between the operated and the contralateral knee, we found that the affected

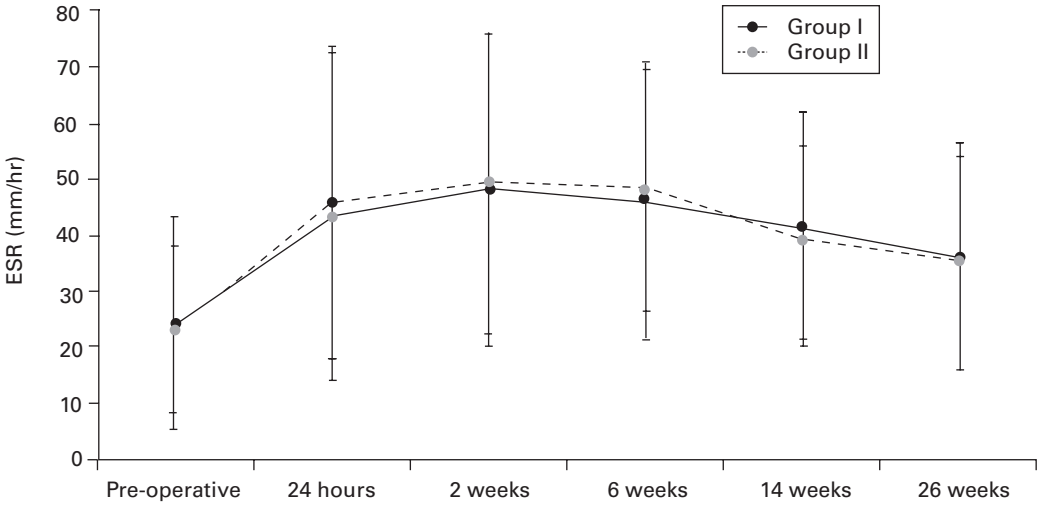

Fig. 3

Plot graph showing the mean ESRs of patients who underwent total knee replacement without synovectomy (group I) or with synovectomy (group II) from pre-operative period to 26-week follow-up (error bars represent SDs).

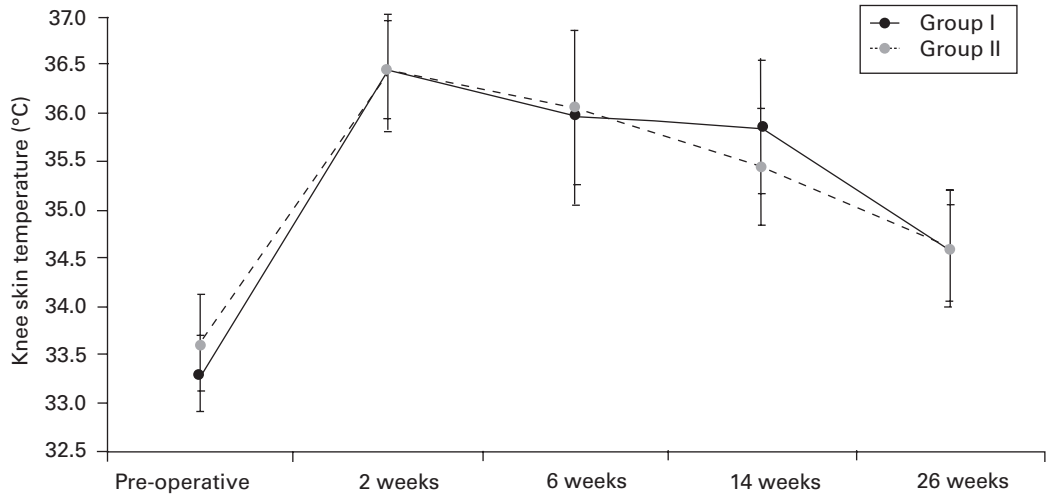

Fig. 4

Plot graph showing the mean knee skin temperature of patients who underwent total knee replacement without synovectomy (group I) or with synovectomy (group II) from pre-operative period to 26-week follow-up (error bars represent SDs).

knee of both groups had a similarly higher temperature from two weeks until six months after surgery, which is in agreement with the findings of Haidar et al.[23]

The clinical outcome of the patients in this series was significantly improved in both groups with no statistical difference between the groups. From two weeks to six months after surgery, we could not demonstrate any difference in clinical outcomes, or in serial IL-6, ESR, CRP measurements and knee temperature, between patients who underwent TKR with or without synovectomy. Thus, the addition of a synovectomy to the TKR undertaken for primary osteoarthritis had no positive effect on post-operative clinical outcomes and knee inflammation, which was different from the results of combined synovectomy with other non-joint replacement procedures.[2-4] It is possible that the soft-tissue trauma arising from TKR induces synovial inflammation which is much greater than that present in the knee pre-operatively. However, the excision of inflamed synovial tissue at the time of TKR failed to shorten the inflammatory process.

The limitations of this study included, firstly, investigating the inflammatory markers from blood samples, and not from the synovial fluid of the affected knee. The inflammatory markers from blood samples may be affected by

unrecognised systemic conditions. However, we attempted to avoid this problem by excluding those patients with systemic inflammatory conditions. Secondly, serial blood samplings were collected at set follow-up times, which might not represent the time of peak level for each inflammatory marker. However, our study primarily intended to compare the changes of the level of each inflammatory marker of patients in both groups rather than to evaluate the peak value of each marker.

Based on these results we conclude that synovectomy at the time of TKR in patients with late-stage primary osteoarthritis does not provide any clinical benefit or reduce the duration of the post-operative inflammatory response.

The authors would like to thank Chulalongkorn Medical Research Center (ChulaMRC) for kindly providing facilities for this research, and B. Deepaisarnsakul and P. Bumrungpanichthaworn for technical assistance.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1. **Altman RD, Gray R.** Diagnostic and therapeutic uses of the arthroscope in rheumatoid arthritis and osteoarthritis. *Am J Med* 1983;75:50-5.
2. **Matsui N, Moriya H, Kitahara H.** The use of arthroscopy for follow-up in knee joint surgery. *Orthop Clin North Am* 1979;10:697-708.
3. **Smiley P, Wasilewski SA.** Arthroscopic synovectomy. *Arthroscopy* 1990;6:18-23.
4. **Klein W, Jensen KU.** Arthroscopic synovectomy of the knee joint: indication, technique, and follow-up results. *Arthroscopy* 1988;4:63-71.
5. **Roch-Bras F, Daurès JP, Legouffe MC, Sany J, Combe B.** Treatment of chronic knee synovitis with arthroscopic synovectomy: long-term results. *J Rheumatol* 2002;29:1171-5.
6. **Ogilvie-Harris DJ, Basinski A.** Arthroscopic synovectomy of the knee for rheumatoid arthritis. *Arthroscopy* 1991;7:91-7.
7. **Kishimoto T.** The biology of interleukin-6. *Blood* 1989;74:1-10.
8. **Krackow K.** *The technique of total knee arthroplasty.* St. Louis: C.V. Mosby; 1990.
9. **Yasgur DJ, Scuderi GR, Insall JN.** Medial release for fixed-varus deformity. In: Scuderi GR, Tria AJ Jr, eds. *Surgical techniques in total knee arthroplasty.* New York: Springer-Verlag, 2002:189-96.
10. **Gonzalez MH, Mekhail AO.** The failed total knee arthroplasty: evaluation and etiology. *J Rheumatol* 2004;12:436-46.
11. **Sussman MD.** Ethical requirements that must be met before the introduction of new procedures. *Clin Orthop* 2000;378:15-22.
12. **Altman R, Asch E, Bloch D, et al; Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association.** Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum* 1986;29:1039-49.
13. **Kellgren J, Lawrence J.** Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494-502.
14. **Laskin RS, Beksac B, Phongjunakorn A, et al.** Minimally invasive total knee replacement through a mini-midvastus incision: an outcome study. *Clin Orthop* 2004;428:74-81.
15. **Plebani M, Piva E.** Erythrocyte sedimentation rate: use of fresh blood for quality control. *Am J Clin Pathol* 2002;117:621-6.
16. **Insall JN, Dorr LD, Scott RD, Scott WN.** Rationale of the Knee Society clinical rating system. *Clin Orthop* 1989;248:13-14.
17. **Pepys MB.** C-reactive protein fifty years on. *Lancet* 1981;1:653-7.
18. **Kushner I, Gewurz H, Benson MD.** C-reactive protein and the acute phase response. *J Lab Clin Med* 1981;97:739-49.
19. **Tanavalee A, Thiengwittayaporn S, Ngarmukos S, Siddhiphongse B.** Contralateral total knee arthroplasty after unilateral surgery in bilateral varus gonathrosis. *J Med Assoc Thai* 2004;87:902-9.
20. **Minetto MA, Oprandi G, Saba L, et al.** Serum interleukin-6 response to elective total hip replacement surgery. *Int Orthop* 2006;30:172-6.
21. **Park KK, Kim TK, Chang CB, Yoon SW, Park KU.** Normative temporal values of CRP and ESR in unilateral and staged bilateral TKA. *Clin Orthop* 2008;466:179-88.
22. **Mehra A, Langkamer VG, Day A, Harris S, Spencer RF.** C reactive protein and skin temperature post total knee replacement. *Knee* 2005;12:297-300.
23. **Haidar SG, Charity RM, Bassi RS, Nicolai P, Singh BK.** Knee skin temperature following uncomplicated total knee replacement. *Knee* 2006;13:422-6.