Comparison of surgical techniques for synovectomy in New Zealand White rabbits with induced inflammatory arthritis

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Objective—To compare effects of synovectomy performed by use of monopolar radiofrequency energy (MRFE) versus mechanical debridement in rabbits with induced inflammatory arthritis.

Animals—25 mature female New Zealand White rabbits.

Procedure—Inflammatory arthritis was induced in both femoropatellar joints of each rabbit. Joints then were treated by mechanical debridement or MRFE treatment or served as sham-operated controls. Rabbits were euthanatized 2 weeks or 3 months after surgery. Biopsy specimens of synovium were analyzed by use of light microscopy.

Results—At 2 weeks after surgery, samples from MRFE-treated joints had fewer plasma cells and more heterophils than the other 2 groups and more lymphocytes than sham-operated controls, whereas samples from mechanically debrided joints had greater numbers of lymphocytes and heterophils than sham-operated controls. At 3 months after surgery, samples from MRFE-treated joints had fewer plasma cells than sham-operated controls, more heterophils than mechanically debrided and sham-operated controls, and more macrophages than mechanically debrided joints. There was no difference in synovial ablation, synovial proliferation, or fibrosis among the 3 groups at 2 weeks or 3 months after surgery.

Conclusions and Clinical Relevance—Analysis of results of this study documented a similar degree of synovial ablation when comparing use of MRFE to mechanical debridement. In rabbits with this method of induced inflammatory arthritis, there were no detectable benefits of MRFE or mechanical debridement on the synovium, compared with results for sham-operated control joints, at 2 weeks and 3 months after surgery for most of the synovial variables evaluated. (*Am J Vet Res* 2004;65:573–577)

Medical treatment of immune-mediated inflammatory arthritis is often successful in managing the processes and clinical signs of the disease.[1-3] In some cases, however, medical management is insufficient to control the inflammatory response and clinical signs persist in 1 or more joints of affected patients. Surgical removal of the synovial lining and thereby its secreted inflammatory mediators has been variably successful in alleviating some of the clinical signs of immune-mediated inflammatory arthritis, especially when used prior to the development of extensive radiographically detectable abnormalities.[4-9] Arthroscopic surgical techniques, including mechanical debridement and laser ablation of the synovium, have been used clinically in affected patients with positive results.[10-14] Evaluation of arthroscopic treatment modalities is increasingly important as arthroscopic synovectomy becomes more commonly used in the surgical management of patients.

Monopolar radiofrequency energy (MRFE) arthroscopic probes are typically much smaller than most arthroscopic mechanical abraders. Small size of MRFE probes may aid substantially in arthroscopic synovial ablation of joints of small humans and small animals with refractory immune-mediated arthropathies and intra-articular synovial neoplasia.

Methods that create an intra-articular antigen-induced antigen-antibody reaction in nonhuman animals most closely mimic the pathogenesis of immune-mediated inflammatory arthritis.[15,16] Such methods have been used to evaluate various treatment modalities (eg, laser treatment and mechanical debridement) that can be used for arthroscopic surgical synovectomy.[17] Intra-articular injection of ovalbumin after immunosensitization produces reliable inflammatory arthritis in rabbits that can be used to create a method for studying immune-mediated inflammatory arthritis and other immune-mediated arthropathies.[17-19]

In in vitro and clinical studies,[20-23] radiofrequency energy has been used to thermally modify intra-articular soft tissue structures, which causes shrinkage of collagenous tissue and articular cartilage. Evaluation of the capsular changes in those studies revealed local synovial ablation when thermal energy was delivered to the joint capsule.[a]

The purpose of the study reported here was to evaluate the effectiveness of MRFE for selective thermal destruction of the synovium in comparison with mechanical debridement. A method of antigen-induced arthritis in rabbits was used, similar to that described in other reports.[17,18] Although arthroscopic synovectomy has been evaluated in larger animals, investigators that have used rabbits prefer an open arthrotomy procedure because of the limited size of the femoropatellar joint.[17,19] For this reason, we selected an

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open procedure instead of arthroscopic application to ensure that the entire synovial surface of each joint was adequately treated without inadvertent treatment of the articular surfaces.

Materials and Methods

Animals—Twenty-five mature female New Zealand White rabbits that ranged from 3.2 to 3.4 kg (mean ± SD, 3.4 ± 0.01 kg) were used in the study. The rabbits were housed and maintained in accordance with protocols established by an institutional animal use and care committee; that committee also approved conduct of the study.

Procedure—Twenty-eight days before surgery, inflammatory arthritis was induced by administering SC injections of 5 mg of ovalbumin in 1 mg of Freund's incomplete adjuvant to each rabbit.[17] Fourteen days later, both femoropatellar joints of each rabbit were clipped, aseptically prepared, and injected with 5 mg of ovalbumin in sterile saline (0.9% NaCl) solution. Fourteen days after the intra-articular injections, all rabbits underwent bilateral femoropatellar arthrotomy.

Food was withheld from all rabbits for 4 hours before surgery. Each rabbit received trimethoprim-sulfamethoxazole (30 mg/kg, SC) before it was anesthetized. Anesthesia was induced with isoflurane and oxygen by use of a mask, and rabbits were then nasotracheally intubated. Anesthesia was maintained by administration of isoflurane and oxygen. Rabbits were placed on a warm-water blanket during surgery to maintain body temperature, and ECG monitoring was performed. All surgical sites were clipped to remove hair and prepared in accordance with conventional aseptic techniques.

All joints were approached through a lateral parapatellar arthrotomy (incision of 3 to 5 cm in length). Preoperative synovial biopsy specimens were obtained distolateral to the patella, a location where the synovium could be easily elevated, and placed into neutral-buffered 10% formalin. By use of a randomized block design (rabbit, treatment, and limb), joints were randomly selected for treatment by use of MRFE or mechanical debridement or to undergo a sham procedure.

Seventeen joints were treated by use of MRFE produced by a radiofrequency energy generator[b] coupled with a monopolar probe[c] at 20 W and 75°C. The probe was submerged in saline solution maintained at room temperature (XX°C) while it was moved in gentle contact with the synovial lining of the joint capsule in a paintbrush pattern. The laterally placed incision provided adequate exposure of the joint to facilitate complete treatment of the synovial lining.

Mechanical debridement was performed in 17 joints by use of a 3.5-mm full-radius resector.[d] Obvious debris from the synovial abrasion was removed by use of active lavage and suction.

The remaining 16 joints served as sham-operated control joints. Arthrotomies were performed as described previously, but joints were not subjected to MRFE treatment or mechanical debridement.

Saline solution maintained at room temperature was used to irrigate joints (during and after synovial ablation as well as sham-operated control joints) before closure of the incision. Surgical incisions were closed in a routine manner by use of monofilament polyglyconate synthetic absorbable suture. All rabbits were administered buprenorphine (0.05 mg/kg, SC) after surgery and at 12-hour intervals thereafter for 48 hours. Each rabbit was fitted with an Elizabethan collar after surgery to prevent self-trauma.

Collection of synovial samples—Rabbits were randomly assigned to 2 time groups. One group of rabbits (n = 13) was euthanatized 2 weeks after surgery, and the other group of 12 rabbits was euthanatized 3 months after surgery.

After rabbits were euthanatized, all femoropatellar joints were inspected to detect macroscopic changes in cartilage. The 13 rabbits euthanatized 2 weeks after surgery constituted 26 joints (9 MRFE, 9 mechanical debridement, and 8 sham-operated), whereas the 12 rabbits euthanatized 3 months after surgery constituted 24 joints (8 MRFE, 8 mechanical debridement, and 8 sham-operated). Full-thickness biopsy specimens of the medial and lateral joint capsule and associated synovium were obtained and placed in neutral-buffered 10% formalin.

Histologic examination—All samples obtained before and after surgery were processed for microscopic examination (ie, embedded in paraffin blocks, sectioned at a thickness of 5 µm, and stained with H&E). Biopsy specimens were evaluated by use of light microscopy and graded by 1 investigator (LP) who was not aware of the treatment administered to each joint. Control slides were evaluated with each sample. Attributes used to evaluate the sections included severity of hemorrhage, number of dilated capillaries, severity of coagulation necrosis, degree of inflammation (divided into relative numbers of plasma cells, lymphocytes, heterophils, and macrophages), degree of synovial proliferation, degree of synovial ablation, and fibrosis. A number was assigned to these attributes by use of a relative scale (0, normal; 1, mild or few; 2, moderate or some; and 3, severe or numerous) that has been described elsewhere.[17]

Statistical analysis—The Mann-Whitney *U* test was used to compare subjective histologic variables among treatment groups (sham-operated, mechanical debridement, and MRFE) within their respective time periods (2 weeks and 3 months). The Wilcoxon signed-rank test was used to compare histologic scores for samples obtained before and after surgery. All differences were considered significant at a value of $P \leq 0.05$. All statistical analyses were performed by use of a commercially available software program.[e]

Results

Animals—None of the rabbits developed lameness or detectable effusion after intra-articular injection of ovalbumin. Minimal lameness and synovial effusion were evident immediately after surgery. Of 50 joints in 25 rabbits, 32 joints of 20 rabbits were included in the results of this study. Sixteen joints (10 rabbits) were available for analysis in the 2-week group, and 16 joints (10 rabbits) were available for analysis in the 3-month group. There was no evidence of cartilage degeneration and minimal gross changes of the joint capsule in the 32 joints included in the study. Complications encountered by the 18 excluded joints were medial patella luxations (14 joints) and insufficient biopsy specimens (4 joints). Twelve joints developed luxations within the first 2 weeks after surgery. All of these joint capsules tore adjacent to the suture line for closure of the arthrotomy incision. Histologic analyses of preoperative samples were consistent with adjuvant-induced arthritis on the basis of evaluation of plasma cells, heterophils, and lymphocytes.

Degree of hemorrhage, capillary dilatation, and coagulation necrosis—We did not detect significant differences among treatment groups (MRFE, mechanical debridement, or sham-operated) for hemorrhage, capillary dilatation, and coagulation necrosis in samples obtained 2 weeks or 3 months after surgery c(**Table 1 and 2**). In rabbits euthanatized 2 weeks after surgery, MRFE-treated samples had more severe scores

Table 1—Median (range) values for histologic grades* of synovial samples obtained before and 2 weeks after surgery from femoropatellar joints of rabbits with antigen-induced arthritis that were subjected to monopolar radiofrequency energy (MRFE) treatment, mechanical debridement, or a sham operations

	MRFE treatment		Mechanical debridement		Sham operation	
Synovial variable	Before (n = 6)	After (n = 6)	Before (n = 5)	After (n = 5)	Before (n = 4)	After (n = 5)
Hemorrhage	0 (0, 0)†	1 (0, 1)	0 (0, 0)	0.5 (0, 1)	0 (0, 0)	0 (0, 0)
Capillary dilatation	0 (0, 0)†	1 (0, 2)	0 (0, 0)†	1 (0, 3)	0 (0, 0)	0 (0, 2)
Coagulation necrosis	0 (0, 0)†	1 (0, 2)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 0)
Plasma cells	1 (0, 3)	1 (1, 1)[a]	1 (0, 2)	1 (0, 1)[b]	1.5 (0, 2)	0 (0, 1)[c]
Lymphocytes	1.5 (1, 2)†[A]	1 (1, 2)[a]	1 (0, 1)[B]	1 (1, 1)[a]	1.5 (0, 2)[C]	1 (0, 1)[b]
Heterophils	0 (0, 0)†	1 (0, 2)[a]	0 (0, 1)	0.5 (0, 2)[b]	0 (0, 0)†	0.5 (0, 2)[c]
Macrophages	1 (0, 2)[A]	1 (0, 2)	0 (0, 0)†[B]	1 (0, 2)	0.5 (0, 2)[A]	1 (1, 1)
Synovial proliferation	0.5 (0, 2)	1 (0, 2)	0 (0, 1)	0.5 (0, 1)	0.5 (0, 1)	0 (0, 2)
Synovial ablation	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)	1 (0, 2)
Fibrosis	0 (0, 0)†	3 (1, 3)	0 (0, 0)†	2 (1, 3)	0 (0, 0)†	2 (2, 3)

*Histologic grading was on a scale of 0 to 3 (0, normal; 1, mild or few; 2, moderate or some; and 3, severe or numerous). †Within a treatment group, score before surgery is significantly ($P < 0.05$) different from score after surgery.
[a-c]Within a row, values after surgery with different superscript letters differ significantly ($P < 0.05$). [A-C]Within a row, values before surgery with different superscript letters differ significantly ($P < 0.05$).
n = Number of joints.

Table 2—Median (range) values for histologic grades* of synovial samples obtained before and 3 months after surgery from femoropatellar joints of rabbits with antigen-induced arthritis that were subjected to MRFE treatment, mechanical debridement, or a sham operation

	MRFE treatment		Mechanical debridement		Sham operation	
Synovial variable	Before (n = 7)	After (n = 6)	Before (n = 6)	After (n = 5)	Before (n = 5)	After (n = 5)
Hemorrhage	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Capillarydilatation	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 0)
Coagulationnecrosis	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Plasma cells	1 (0, 2)†	0 (0, 0)[a]	0.5 (0, 1)†	0 (0, 0)[a]	1 (0, 1)	0 (0, 1)[b]
Lymphocytes	1 (0, 2)†	0 (0, 1)	1 (0, 2)	0 (0, 1)	0.5 (0, 2)	0 (0, 2)
Heterophils	0 (0, 3)	0 (0, 3)[a]	0 (0, 1)	0 (0, 0)[b]	0 (0, 1)	0 (0, 0)[b]
Macrophages	0.5 (0, 2)	0 (0, 3)[a]	0 (0, 2)	0 (0, 0)[b]	0 (0, 2)	0 (0, 0)[a]
Synovial proliferation	0 (0, 1)	0 (0, 1)	0 (0, 2)	0 (0, 1)	0 (0, 0)	0 (0, 0)
Synovial ablation	0 (0, 0)	1 (0, 2)	0 (0, 0)†	0 (0, 2)	(0, 0)	0 (0, 2)
Fibrosis	0 (0, 1)	0 (0, 1)	0 (0, 1)	1 (0, 2)	0 (0, 0)	0 (0, 1)

See Table 1 for key.

for all 3 categories, compared with scores for samples obtained before surgery, whereas mechanically debrided samples had higher scores only for capillary dilatation, compared with scores for samples obtained before surgery. In rabbits euthanatized 3 months after surgery, there were no significant differences in any of the 3 categories between samples obtained before and after surgery for the 3 treatment groups.

Cellular infiltrates—In rabbits euthanatized 2 weeks after surgery, we did not detect significant differences in cellular infiltration of lymphocytes or macrophages between MRFE and mechanically debrided groups, whereas samples for the mechanically debrided group had significantly better histologic scores with regard to cellular infiltration of plasma cells and heterophils, compared with scores for MRFE-treated samples (Table 1). Except for macrophages, sham-operated control joints had better histologic scores 2 weeks after surgery than the MRFE-treated and mechanically debrided samples with regard to infiltration of plasma cells, lymphocytes, and heterophils. Samples obtained 2 weeks after surgery from MRFE-treated joints had significantly more heterophils and significantly fewer lymphocytes, compared with values for the samples obtained before surgery.

Samples obtained 3 months after surgery from MRFE-treated joints had significantly more severe histologic scores with regard to cellular infiltration of heterophils and macrophages, compared with values for samples from mechanically debrided joints (Table 2). There were significantly fewer plasma cells and lymphocytes in MRFE-treated samples obtained 3 months after surgery, compared with values for samples obtained before surgery.

Degree of synovial ablation, proliferation, and fibrosis—We did not detect significant differences among the 3 treatment groups for synovial ablation, proliferation, and fibrosis in samples obtained 2 weeks or 3 months after surgery (Table 1 and 2). In samples obtained 2 weeks after surgery, all 3 treatment groups had significantly higher (ie, more severe) histologic scores for fibrosis, compared with scores for samples obtained before surgery. In samples obtained 3 months after surgery, only samples for mechanically debrided

joints had greater synovial ablation, compared with values for samples obtained before surgery.

Discussion

In contrast to results of another study[17] in which investigators evaluated effects of laser synovectomy, results of the study reported here revealed that MRFE treatment did not have significant advantages over mechanical debridement for synovectomy in these rabbits. In that other study, investigators used subjective histologic scoring to document a significant difference between the mechanically debrided group, compared with laser and electrocautery groups, at 2 weeks and 3 months after surgery. The mechanically debrided group had poorer scores overall with respect to hemorrhage, infiltration of plasma cells, number of lymphocytes, synovial ablation, and joint capsular defects.[17] Although a direct comparison cannot be made, the **holmium:yttrium-aluminum-garnet (Ho:YAG)** laser appears to be better for synovial ablation than MRFE, given that the Ho:YAG laser resulted in significantly better histologic scores than mechanical debridement. In the study reported here, MRFE treatment did not cause such a difference, despite use of an identical method for inducing inflammatory arthritis. The difference between the Ho:YAG laser and MRFE is probably attributable to several factors. First, penetration of the Ho:YAG laser for soft tissue (1 mm) is less than penetration for the MRFE technique (3 to 5 mm).[21] This deeper penetration of MRFE can result in more coagulation, increased healing time, and a higher likelihood that deeper tissues, such as muscle, would be affected to cause a subsequent increase in inflammatory infiltration. Additional studies are needed to compare effects of the Ho:YAG laser and MRFE treatment.

In addition, the degree of synovial ablation caused by MRFE treatment and mechanical debridement did not differ from sham-operated control joints at 2 weeks or 3 months after surgery in the study reported here. However, cellular infiltration in MRFE-treated and mechanically debrided joint capsules was more severe 2 weeks after surgery, compared with infiltration in joint capsules of sham-operated control joints, although the cellular infiltration caused by MRFE treatment and mechanical debridement improved 3 months after surgery, compared with values for sham-operated control joints.

Our study had a design similar to that of other studies[17,19] in which investigators used antigen-induced arthritis in rabbits to evaluate various modalities of surgical synovectomy. However, complications encountered in our study differed from those in the other reports. First, we detected a high number of patellar luxations, which caused us to exclude those joints from analysis. Although arthrotomy undoubtedly made the joints more susceptible to luxation, the high number of luxations probably was not attributable to surgical manipulation alone because there was an additional rabbit that had a luxated patella before the start of the study. In addition, the slat construction of the floors of the rabbits' cages allowed their feet to occasionally slip between the slats and become entrapped when they attempted to move quickly around the cage after surgery. The degree of forced motion at the incision after surgery may have resulted in sufficient strain along the suture line to allow tearing along the lateral retinaculum and subsequent medial patellar luxation.

In another study,[24] investigators documented that the failure strength of MRFE-treated joint capsules is less than that of control capsules at 0 to 14 days after treatment. All luxations in the study reported here were evident by 14 days after surgery. However, the fact that approximately equal numbers of joints in the sham-operated, MRFE-treated, and mechanically debrided groups developed luxations makes this explanation less likely. Three of these luxated joints received mechanical debridement, 4 received MRFE treatment, and 4 underwent sham surgical procedures.

The study reported here also differed from some other studies that used rabbits with antigen-induced arthritis in that although antigen-induced arthritis was histologically confirmed, lameness and joint effusion were minimal after immunosensitization. Grossly, intra-articular structures appeared normal before surgery. This difference can be explained by the decreased degree of immunosensitization used in our study, compared with the degree used in other studies. Other investigators[18,19,25] identified substantial effusion, lameness, and gross pathologic changes following immunosensitization. Investigators in those studies administered 2 doses of ovalbumin, ID, prior to intra-articular injection. Some rabbits in those studies did not receive intra-articular injections; however, skin testing was performed prior to surgery to confirm sensitization. We used exactly the same protocol that was used in another study[17]; although the investigators of that study did not comment on the degree of lameness, they did not detect significant differences in gross pathologic changes among control, sham, and treated groups at 2 weeks or 3 months after surgery. Similar to that study, lymphocytes and plasma cells predominated in synovial samples obtained before surgery in the study reported here. Heterophils were also not found in the synovium of the nonoperated control stifles with immune-mediated arthritis in that study.[17] Detection of plasma cells, lymphocytes, and macrophages in the preoperative synovium in that study confirmed a chronic immune-mediated process, which is consistent with the method we used.

Interestingly, despite synovectomy accomplished by MRFE treatment or mechanical debridement, both of these groups had synovial ablation scores that were similar to scores for sham-operated control joints 2 weeks and 3 months after surgery. The 2 most likely explanations for this similarity in ablation scores are the regrowth of the synovial membrane in the MRFE-treated and mechanically debrided groups by 2 weeks after surgery or overly conservative synovectomy with either technique leading to only modest removal of synovium during surgery. Because biopsy specimens were not obtained immediately after synovectomy, it is unclear which of these 2 explanations is the most likely for the low synovial ablation scores.

Developing safe and effective modalities for arthroscopic synovectomy is crucial for surgical man-

agement of immune-mediated inflammatory arthritis that is refractory to medical treatment. This is especially true for early immune-mediated inflammatory arthritis in which surgical synovectomy may substantially delay the progression of disease.[26,27] In small joints or joints that are difficult to navigate, the potential technical advantages of the MRFE probe for ablation of synovium in narrow spaces may necessitate its use over traditional mechanical debridement.

Studies[4-6,9,10] have documented continued progression of immune-mediated inflammatory arthritis despite synovectomy and have alternatively suggested that the alleviation of clinical signs may be attributable to spontaneous remission of immune-mediated inflammation, rather than as a result of surgical intervention. Thus, long-term prospective studies are needed to determine efficacy of any surgical modality.

In the study reported here, MRFE treatment did not result in beneficial effects for synovectomy similar to those of an Ho:YAG laser reported in another study.[17] Methods used to induce arthritis in nonhuman animals are limited in their ability to mimic human diseases; therefore, direct extrapolation of results should be avoided.[28] Additional studies that compare MRFE treatments to laser and electrocautery techniques are needed to determine the most effective thermal treatment modality for synovectomy.

[a]Hayashi K, Department of Small Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, MI: Personal communication, 2002.
[b]Vulcan EAS generator, Smith & Nephew Inc, Endoscopy Division, Andover, Mass.
[c]Monopolar mini TAC-S probe, Smith & Nephew Inc, Endoscopy Division, Andover, Mass.
[d]Full radius resector C9800, Linvatec Corp, Largo, Fla.
[e]ANOVA SAS, version 7.1, SAS Institute Inc, Cary, NC.

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