American Journal of Hematology 27:26-29 (1988)

Intraarticular Methylprednisolone Therapy in Hemophilic Arthropathy

R. Shupak, J. Teitel, M.B. Garvey, and J. Freedman
St. Michael's Hospital, University of Toronto, Toronto, Canada

This small pilot study examined the use of intraarticular methylprednisolone in hemophilic synovitis. Nineteen joints in ten adult hemophiliacs were studied. There was subjective improvement at 24 hr following injection in 79% of joints injected, and the improvement persisted up to 8 wk in 58%. The number of hemarthroses decreased following intraarticular steroids (mean of 7.7 bleeds in the 8 wk prior to injection versus a mean of 1.9 bleeds in the 8 wk following injection). Similarly the amount of clotting factor used for the injected target joint decreased from a mean of 7,616 units to 2,315 units postinjection ($p < .001$). Improvement correlated with presence of synovitis but not with radiologic stage of the joint. Aspirated synovial fluids were analyzed and showed characteristics consistent with low-grade inflammation. These preliminary observations suggest that intraarticular corticosteroid injection may be a useful therapeutic tool in the medical management of hemophilic arthropathy.

Key words: synovitis, hemophilia, corticosteroids, hemarthrosis

INTRODUCTION

Large joints are the most common sites of hemorrhage in hemophilia. Recurrent joint bleeding results in a proliferative synovitis resembling that seen in rheumatoid arthritis [1,2].The synovium is friable and highly vascular, predisposing to further bleeding in the hemophilic joint. If bleeding into the joint persists, the synovitis is frequently followed by a more destructive and debilitating arthropathy which is a major source of morbidity for the hemophiliac patient. While intraarticular corticosteroids are commonly used to control synovitis in inflammatory joint disease of other etiologies [3], the value of this therapeutic approach in the treatment of hemophilic arthropathy is unknown. To our knowledge, there are no previous reports of intraarticular steroid injections in hemophilic arthritis. This report describes the results of a small pilot study of the use of intraarticular methylprednisolone in controlling synovitis and recurrent hemarthroses in 19 joints of ten adult hemophiliacs.

PATIENTS AND METHODS

Patients

Ten adult hemophiliacs aged 25–38 yr were studied. Seven subjects had hemophilia A and three had hemophilia B; eight patients had severe hemophilia (factor VIII or IX level less than 1% of normal) and two were mild hemophiliacs. No patient had inhibitors to coagulation factors. Joints were radiologically staged according to Arnold and Hilgartner [4].

Indications for intraarticular methylprednisolone were (1) chronic synovitis of at least 2 months duration, as evidenced by heat, swelling, and tenderness of the joint; (2) recurrent hemarthroses not responding to coagulation factor replacement, rest, and physiotherapy; and (3) advanced arthropathy without signs of active inflammation. Seventeen of the 19 joints injected fulfilled criteria 1 and/or 2; in one patient, two joints fulfilling criterion 3 alone were injected. Joints injected included knees (ten), elbows (four), shoulders (three), ankle (one), and wrist (one). Four of the joints were reinjected at intervals of not less than 3 months.

Procedure

Following cleansing of the skin with antiseptic, synovial fluid was aspirated if present and methylpredniso-

Received for publication March 16, 1987; accepted July 9, 1987.

Address reprint requests to Dr. John Freedman, Blood Bank, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, Canada, M5B 1W8.

TABLE I. Subjective Response to Intraarticular Methylprednisolone

Joint	No. injected	No. improved at 24 hours	4 weeks	8 weeks
Knee	11	9	6	6
Elbow	3	3	3	2
Shoulder	2	2	2	2
Ankle	1	0	0	0
Wrist	1	1	1	1
Total	19	15 (79%)	12 (63%)	11 (58%)

lone was then injected with the same needle. A 23-gauge needle was used for injections into elbow joints and a 21-guage needle for all other joints. All intraarticular injections were performed by an experienced rheumatologist (R.S.). The choice of corticosteroid agent and the dosages used were based on our experience with intraarticular treatment of other inflammatory arthritides; 80 mg of methylprednisolone was injected into knees and 40 mg into all other joints. Patients were simultaneously given coagulation factor replacement sufficient to achieve 30–50% circulating factor levels. Following injection into lower limb joint, weight-bearing was avoided for 24 hr; no specific precautions were taken for other joints.

Laboratory Evaluation

Aspirated synovial fluid was analyzed for total and differential leukocyte count and for synovial fluid glucose, protein and complement C3 and C4 content. The synovial fluids were also cultured for microorganisms and examined under polarized light microscopy for crystals.

Evaluation of Outcome

A "good response" was defined as (1) subjective improvement in overall joint function and (2) improvement in symptoms and/or signs of inflammation (pain, swelling, and warmth) as assessed either by physical examination or reliable history. All ten patients were either seen or called by telephone 8 weeks following intraarticular injection. Subjective assessment is available on all ten patients (19 joints).

In seven patients (11 joints) treatment diaries were considered reliable for documentation of frequency of hemarthroses and amount of factor used. The frequency of hemarthrosis and the amount of coagulation factor used in the 8-wk periods preceding and following intraarticular injection were compared. Although the range of motion of joints was documented in all patients prior to injection, insufficient data was available at the 8-week postinjection follow-up, and these data have therefore not been included.

RESULTS

Subjective Improvement

Table I shows the number of patients noting subjective improvement in symptoms and signs following intraarticular methylprednisolone injection. Twenty-four hours after treatment, improvement was reported in 79% of joints injected; at 8 wk after treatment, continued subjective improvement was reported in 58% of the treated joints. In no patients were hemarthrosis or other adverse effects of intraarticular injection observed.

Frequency of Bleeds and Factor Replacement

In the seven patients with reliable diaries (11 joints injected), the mean frequency of hemarthroses in the 8 wk anteceding intraarticular steriod injection was 7.7 (range three to 14); in the 8 wk following intraarticular injection the mean frequency of hemarthroses in these subjects was 1.9 (range zero to four bleeds) ($p < .001$; Student's t-test).

The amount of clotting factor used specifically for the injected target joint decreased from a mean of 7,616 units (range 960–17,600) in the 8 wk preceding injection to 2,315 units (zero to 6,940) in the post treatment period ($p < .001$).

Radiological Staging

Of the 19 joints injected, radiographs were available for staging in 15. Ten of the 15 were either stage I, II or III, ie, had preservation of articular cartilage. Seven of the ten had clinical evidence of synovitis and all seven of these showed clinical improvement postinjection. Five joints were stage IV or V, ie, had loss of articular cartilage; of these, three had clinical synovitis and all three improved postinjection.

Synovial Fluid Analysis

Synovial fluid was aspirated from 11 joints prior to injection. One synovial fluid was grossly hemorrhagic, five were serosanguinous, four were serous and one was viscid. Differential leukocyte counts were available from seven synovial fluids; the mean cell distribution was

lymphocytes 75%, monocytes 21%, and neutrophils 4%. Joint fluid globulin exceeded the upper limit of the normal range (30 g/liter) in all six fluids tested (mean 43.3 g/liter; range 35–55 g/liter). Levels of complement C3 were decreased in each of five fluids tested, and C4 was decreased in three of five fluids. Synovial fluid glucose content was normal in all of six tested and calcium pyrophosphate crystals were not seen microscopically in any of the 11 fluids examined. All 11 joint fluids were sterile on culture.

DISCUSSION

Although the natural history of hemophilic arthritis does not follow a single pattern, repetitive hemarthroses usually lead to the development of proliferative synovitis. A destructive arthropathy frequently follows, characterized by osteopenia, cystic change in subchondral bone, cartilage destruction, and joint collapse [5,6]. When such a "target joint" develops, therapeutic intervention is necessary to break the cycle of hemarthrosis aggravating synovitis and the associated hypervascularity within the synovium predisposing to further bleeding into the joint. Treatment of an affected target joint includes rest, splinting, muscle-strengthening exercises, and prophylactic coagulation factor replacement, but despite these measures, pathologic and clinical deterioration is frequent. Attempts to remove the hypervascular synovium and induce hemostasis in the joint have included chemical, radioactive, and surgical synovectomy [7]. Surgical synovectomy, the most commonly employed approach, requires prolonged convalescence and frequently results in restricted joint function [8,10].

The inflammatory nature of hemophilic synovial fluid was evidenced by a low leukocyte count with predominance of lymphocytes and mononuclear cells (suggesting low-grade inflammation), decreased synovial fluid complement, and increased gamma globulin. There are a number of similarities between the synovitis of inflammatory joint diseases, such as rheumatoid arthritis, and that seen in hemophilia. In both conditions, pathologic changes include an inflammatory mononuclear cell infiltrate within the synovium, synovial hyperplasia, synovial villous hypertrophy, and pannus formation [6]. In contrast to the predominance of polymorphonuclear leukocytes in rheumatoid arthritis synovial fluid, however, the synovial fluid in hemophilic joints predominantly contains lymphocytes and mononuclear cells.

Extensive clinical experience [3,11,12] has shown both subjective and objective improvement in inflammatory arthritic joints following intraarticular injections with poorly soluble corticosteroid esters, eg, methylprednisolone. Although duration of response to intraarticular steroid in inflammatory arthritis is variable, the anti-inflammatory effects often persist for weeks or months [3]. The similarities described above between the synovitis of inflammatory joint disease and that of hemophilia prompted our use of intraarticular methylprednisolone to control synovitis in hemophilic joints.

It is possible that the clinical response was partly due to joint aspiration rather than methylprednisolone instillation. However, the observation that approximately 60% of treated joints maintained their initial improvement for up to 8 wk compares favorably with the response to intraarticular corticosteroids in inflammatory arthritides of other etiologies [3]. In addition to subjective improvement in treated hemophilic joints, a significant decrease in the frequency of bleeding into the joint and a corresponding decrease in coagulation product utilization were observed. Furthermore, the conclusion that improvement was due to the local antiinflammatory effect of the corticosteroid ester is supported by the observation that response correlated with clinical evidence of synovitis at the time of injection. Radiological stage of the joint was not correlated with response to the injection. Two patients with target joints showing clinical and laboratory synovitis but normal x-rays demonstrated limited joint function prior to, but normal joint function following, intraarticular steriod. It may be hypothesized that administration of intraarticular steroids prior to occurrence of joint damage may, by controlling synovitis, prevent progression of a target joint to the more destructive arthropathy.

Septic arthritis is a potentially serious complication of intraarticular corticosteroid injection, but is rare, occurring in 0.16% of patients [13]. Crystal-induced synovitis is a more common complication (1–2%) but has less serious sequelae [13]. Neither of the above complications was observed in the current small series. Adverse pharmacological effects, such as osteonecrosis of juxtaarticular bone and complications of systemic steroid absorption, are not problems with single or infrequent injections. No problems with local bleeding due to joint injection were observed in this study.

The preliminary observations in this small pilot study suggest that intraarticular corticosteroid injection may be a useful adjunctive therapeutic measure in the medical management of hemophilic synovitis. The use of this therapeutic approach in the early stages of the synovitis, when radiographs are normal, may prevent progression to a more destructive arthropathy. With cartilage loss (radiological stages IV, V), intraarticular steroids were still found to be beneficial. However, long-term benefits remain uncertain. The intraarticular injections were well tolerated and were not associated with adverse effects. More detailed studies evaluating objective changes in joint range-of-motion and response to physiotherapy in

hemophiliacs treated with intraarticular methylprednisolone injections are warranted.

ACKNOWLEDGMENTS

The authors would like to acknowledge the assistance of Ms. A. Harrington, nurse coordinator of the Hemophilia Comprehensive Care Program in our hospital, and also to thank Ms. M. Vranic for typing the manuscript.

REFERENCES

1. Arnold WD: Synovectomy. Ann NY Acad Sci 240:338, 1974.
2. Hilgartner MW: Degenerative joint disease. Ann NY Acad Sci 240:340, 1974.
3. Gray RG, Tenenbaum J, Gotleib NC: Local corticosteroid injection treatment in rheumatic disorders. Semin Arthritis Rheum 10:4, 1981.
4. Arnold WD, Hilgartner MW: Hemophilia arthropathy: Current concepts of pathogenesis and management. J Bone Joint Surg 59A:287, 1977.
5. De Palma AF: Hemophilic arthropathy. Clin Orthop 52:145, 1967.
6. Gilbert MS: Musculoskeletal manifestations of hemophilia. Mt Sinai J Med NY 44:339, 1977.
7. Gamba G, Grignani G, Ascari E: Synoviorthesis versus synovectomy in treatment of recurrent hemophilic hemarthrosis: Long-term evaluation. Thromb Haemost 45:127, 1981.
8. Kay L, Stainsby D, Buzzard B, Fearno M, Hamilton PJ, Owen P, Jones P: The role of synovectomy in management of recurrent hemarthroses in hemophilia. Br J Haematol 49:53, 1981.
9. Mannucci PM, Francis RD, Torri G, Pietrogrande V: Role of synovectomy in hemophilic arthropathy. Isr J Med Sci 13:983, 1977.
10. Gilbert MS: Reconstructive surgery in the hemophiliac. Mt Sinai J Med NY 44:374, 1977.
11. Stolzer BC, Barr JH, Jr, Margolis HM, Crittenden JO, Eisenberg CH, Jr. Intra-articular injections of adrenocorticosteroids in patients with arthritis. Penn Med J 65:911, 1962.
12. Hollander JL, Jessar RA, Brown EM, Jr: Intrasynovial corticosteroid therapy: A decade of use. Bull Rheum Dis 11:239, 1961.
13. Hollander JL: Arthrocentesis technique and intrasynovial therapy. In McCarty DJ (ed): "Arthritis and Allied Conditions." Philadelphia: Lea and Febiger, 1985, pp 541–543.