CONCISE REPORT

Autoplex Versus Proplex: A Controlled, Double-Blind Study of Effectiveness in Acute Hemarthroses in Hemophiliacs With Inhibitors to Factor VIII


In view of uncontrolled observations and anecdotal reports suggesting that the activated PCC, Autoplex, was much more effective than standard (non-activated) PCC in controlling bleeding in hemophiliacs with inhibitors, a controlled double-blind study was designed to compare the effectiveness of Autoplex and Proplex. Acute hemarthrosis was chosen for study as this common but non-life-threatening lesion lends itself well to controlled study. A single dose of "unknown" product (Autoplex 75 FECU/kg; Proplex 75 FIX U/kg) was given, and effectiveness was judged at 6 hr. By all criteria of efficacy, there were no significant differences between the products. It is noteworthy that a single dose of PCC was judged effective in 50% of episodes, a figure that is consistent with other published clinical trials. In this model, no additional benefit was derived from using the activated PCC, Autoplex, in either dosage.

Approximately 15% of individuals with hemophilia A develop antibodies (inhibitors) to factor VIII:C. The majority of these inhibitor patients are high titer antibody formers, demonstrating a marked anamnestic response following infusion of any FVIII-containing material. Treatment of bleeding episodes in such individuals remains difficult. Over the past 2 decades, a number of therapeutic approaches have been tried, including the use of massive infusions of human FVIII concentrate, various immunosuppressive regimens, porcine and bovine FVIII concentrates, and attempted "bypassing" of the inhibitor with prothrombin complex concentrates (PCC). While the precise mechanism of such "bypass" action remains uncertain, PCCs appear to be effective in controlling some (but not all) bleeding episodes. In a controlled, double-blind trial in which two commercially available PCCs (Cutter’s Konnye and Hyland’s Proplex) were compared to an albumin placebo, a single dose of either of the PCCs was effective in the treatment of acute hemarthrosis approximately 50% of the time, whereas the placebo was effective 25% of the time. In another controlled, double-blind study, Immuno’s FEIBA (an activated PCC) was effective in controlling joint or muscle hemorrhage 62% of the time, whereas Immuno’s nonactivated PCC was effective in 50% of the episodes. In January 1980, a new activated PCC, Autoplex, was licensed for use in inhibitor patients in this country. While Autoplex is considerably more costly than the nonactivated PCCs, uncontrolled observations and anecdotal reports suggested that Autoplex might be much more effective than nonactivated PCCs in controlling bleeding in patients with inhibitors, especially for surgery or life-threatening hemorrhage. However, there has been no controlled, double-blind study of Autoplex versus standard (nonactivated) PCC. Hyland Laboratories, the manufacturers of Autoplex, initiated a trial design and enlisted the directors of five U.S. hemophilia centers to participate in the study. Hemarthrosis was chosen for study because this common but non-life-threatening lesion lends itself well to controlled study. The study design, conduct, and results are presented here.

MATERIALS AND METHODS

Study Design

Bleeding episodes evaluated were acute hemarthroses only, involving knees, ankles, elbows, and wrists. These joints were selected as they are the most common sites of bleeding in hemophiliacs, and also because range of motion of these joints could be easily measured. When acute hemarthroses occurred, study subjects infused themselves (or were infused) with a single dose of the next unknown product on their assignment sheet.

The study group was comprised of the following investigators and institutions: J. M. Lusher, M.D. and A. I. Warrier, M.B., B.S., Children’s Hospital of Michigan, Wayne State University School of Medicine, Detroit, MI; P. M. Blatt, M.D., C. McMillan, M.D., H. Roberts, M.D. and G. C. White, M.D., University of North Carolina School of Medicine, Chapel Hill, NC; J. A. Penner M.D., Michigan State University College of Human Medicine, East Lansing, MI; L. M. Aledort, M.D. and M. Diaz, M.D., Mount Sinai School of Medicine, New York, NY; P. H. Levine, M.D. and D.B. Brettler, M.D., Worcester Memorial Hospital and University of Massachusetts Medical School, Worcester, MA; A. Y. Rao, Ph.D., D. A. Whitehurst, M.B.A., and P. V. Pfieferia, M.S., Research Triangle Institute, Research Triangle Park, NC (Statistical Methodology and Analysis Center); and M. L. Lee, Ph.D. and H. Kingdon, M.D., Hyland Therapeutics Division, Travelon Laboratories, Inc.

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The three “unknown” products selected were Proplex, in a dosage of 75 FIX U/kg, which is the dosage of nonactivated PCC used in most centers to treat hemophiliacs with inhibitors, and Autoplex in two dosages, 50 and 75 FVIII correctional units (FECU)* per kg. Two dosages of Autoplex were chosen, as no clear guidelines had been established regarding appropriate dosage for treating acute hemarthroses in inhibitor patients, and various anecdotal reports had used one or the other of these dosages. In view of the substantial cost of the product ($1.11 per FECU), it was thought to be important to establish whether a lower dosage (50 FECU/kg) was as effective as 75 FECU/kg.

Arbitrarily assuming that there might be a 25% difference in efficacy between the products, with approximately 50% of episodes responding favorably to nonactivated PCC and 75% responding to activated PCC, it was determined that 90 treatment episodes would be sufficient to show such a difference.

Six hours was selected as the endpoint for the trial, as it was our general impression that acute hemarthroses in non-inhibitor patients treated with FVIII had subjective and objective improvement by 6 hr, and also because 6 hr had been used as the endpoint in the earlier double-blind study comparing Konyne, Proplex, and albumin placebo, thus allowing some comparisons with results in that trial.4

Adverse reactions were carefully monitored, so that the study could be terminated at any point if it was decided that the risk-benefit ratio was too great.

Patient Population

Each of the five participating hemophilia centers selected six hemophiliacs with inhibitors for participation in the trial. Criteria for selection included: (1) an inhibitor titer of at least 2.0 Bethesda units; (2) anticipation of fairly frequent bleeding into joints (i.e., patients who had not bled into a joint during the preceding 12 mo were not considered for the trial); (3) the absence of severe liver disease; and (4) patient reliability.

Each subject selected was called to his treating center for an explanation of the trial. Subjects were given the opportunity to ask questions and were then asked to read and sign the consent form. Each center then submitted a list of their consenting patients’ identification numbers and weights to the statistical center, Research Triangle Institute, Research Triangle Park, NC.

The majority of patients entered in the trial were on home treatment and received the unknown products at home. However, some individuals received the unknown products at a hemophilia center.

Concentrates Evaluated

Hyland Therapeutics Division, Travenol Laboratories, Inc. (Glendale, CA) provided nonactivated PCC (Proplex) and activated PCC (Autoplex) free of charge for the study. The lots used were prepared in 1981. Each bottle of concentrate contained approximately 750 U of FIX (in the case of Proplex) or 500 or 750 FECU (in the case of Autoplex). Two lots of Autoplex were used, so that the number of bottles for the high-dose Autoplex and low-dose Autoplex “unknowns” were the same for a particular subject. All bottles were identical in appearance and were labeled by a number code only.

Coding and Randomization Scheme

Each bottle was labeled with an Arabic-Roman number code. A sequence of three treatments was assigned to each patient in random order by the statistical center. Each group of three treatments included Proplex, 75 FIX U/kg, Autoplex, 75 FECU/kg, and Autoplex, 50 FECU/kg.

The statistical center sent directions for each patient to the respective participating center, including a list of sequence numbers for each patient and the number of bottles to be used by each patient (i.e., the appropriate dose per treatment for each, expressed in bottles of coded product). The bottles were then distributed to each center.

Study Protocol

Directions and reporting forms were reviewed with all center personnel who would be directly involved and with all patients. Personnel and patients were instructed in the proper use of the goniometer to measure range of motion of the knee, ankle, elbow, and wrist in the sagittal plane and were also instructed in the proper recording of values. Each patient was provided with a goniometer. Each subject was also provided with a set of drawings and brief written descriptions for measuring these four joints, and each was advised to look at these again whenever measuring a particular joint.

All were instructed that whenever there was an acute hemorrhage into a knee, ankle, elbow, or wrist, the subject or center personnel should fill in baseline subjective and objective data on the treatment episode report form. Subjective data included the degree of joint pain (severe, moderate, mild, or none), and objective data consisted of the degree of joint mobility as measured with a goniometer. Any evidence of chronic joint disease, as manifest by bogginess of the joint or prior limitation of motion (before the episode being evaluated), were also recorded.

The subject then received the next unknown product on his assignment sheet. Subjective and objective data were again recorded at 1 hr and 6 hr after infusion. At 6 hr, which was the endpoint for the trial, the patient was asked to judge whether the unknown product had been very effective, slightly effective, not effective at all, or whether he was not sure. Completed forms were sent to the statistical center, and all data were entered into the computer. The code was not broken until the completion of the study.

RESULTS

Although 6 patients from each of the 5 centers had been selected for this trial, not all 30 patients had bleeding into a knee, elbow, ankle, or wrist during the study period. Twenty-six patients with hemophilia A and FVIII inhibitors received “unknown” products for acute hemarthroses on one or more occasions, for a total of 82 treatment episodes. High-dose (75 FECU/kg) Autoplex was given in 29 episodes, low-dose (50 FECU/kg) Autoplex in 27, and Proplex (75 FIX U/kg) in 26.

Results were tabulated and analyzed for all 82 episodes. As shown in Table 1, for 78 episodes in which initial joint pain was reported, improvement in joint pain was noted at 6 hr in 53.8% of episodes treated with high-dose Autoplex, 51.9% of episodes treated with low-dose Autoplex, and 56.0% of those treated with Proplex. There was no significant difference between any of the three products.

Similarly, in all other criteria of efficacy, there were no significant differences between the products. For 71 episodes with initial limitation of motion, improvement in joint mobility was noted at 6 hr in 51.9% of episodes treated with high-dose Autoplex, 47.8% of those...

*One FECU is defined as that amount of reconstituted Autoplex which, when added to FVIII-deficient plasma, will correct the ellagic acid APTT of that plasma to 35 sec.
treated with low-dose Autoplex, and 42.9% of those treated with Proplex. If one looks at perceived need for a second treatment with a "known" product (i.e., treatment with the subject's usual product), 31.0% of those initially treated with high-dose Autoplex were treated a second time, 22.2% initially treated with low-dose Autoplex received a second ("known") treatment, as did 30.8% of those receiving Proplex. The overall perceived effectiveness of a single dose of Autoplex (at either dosage) was no better than that of Proplex (see Table 1).

The data were analyzed using simple chi-square test as well as through more complex approaches, considering the patient as a factor. The latter approaches did not provide any more information than those provided by the chi-square test.

An analysis of immediate adverse reactions occurring after the unknown products indicated a few minor reactions, but no major complications. Occasional reactions reported with all three unknowns included transient dizziness or headache. One patient complained of severe abdominal pain while receiving Autoplex (this subsided when the infusion was discontinued), while one other had a transient drop in blood pressure to 80/50 during the infusion of Autoplex.

**DISCUSSION**

Reports of uncontrolled observations\(^6,7\) suggest that Autoplex is superior to the so-called nonactivated PCCs in management of bleeding episodes in hemophiliacs with inhibitors. However, the need for a controlled, double-blind study was obvious. This study was designed to question the relative effectiveness of a single dose of nonactivated PCC versus a single dose of Autoplex (in two selected dosages) in the treatment of acute hemorrhages. The latter non-life-threatening bleeding episodes provide the best current model in which to determine efficacy of therapeutic strategies in hemophiliacs with inhibitors. Of the four variables analyzed in this trial, pain (listed as "symptomatic improvement" in Table 1) and overall perceived effectiveness were considered by most participants to be the most reliable indicators of efficacy. It is noteworthy that a single dose of PCC was judged effective in 50% of episodes, a figure that is consistent with other published clinical trials.\(^4,5\) No additional benefit was derived from using the activated PCC, Autoplex (in either dosage), in this model.

One cannot extrapolate these findings beyond the trial situation, however. Since it is recognized that bleeding episodes in patients with inhibitors do not respond to any mode of treatment as well as non-inhibitor patients respond to FVIII, perhaps the trial design should have incorporated two doses of each "unknown" PCC,\(^8,9\) with the second dose being given 6–8 hr after the first. In addition, it should be noted that no attempt was made to exclude chronic "target" joints from this trial. Such joints are prone to recurrent bleeding and such bleeding episodes may respond suboptimally to any form of treatment.\(^10,11\)

Similarly, one cannot equate acute hemorrhages and other hemorrhagic phenomena. Clearly, a number of independent clinicians and observers have been impressed with the efficacy of Autoplex in controlling bleeding in acute surgical situations, head injury, and tongue lacerations.\(^6,7,12-14\) While such situations cannot be randomized in a double-blind controlled trial, and while dosage requirements and response times may vary, the benefits of Autoplex in controlling such serious, life-threatening, open types of hemorrhage are no doubt real.

Future trials are needed to help establish the role of activated PCCs in the management of joint bleeding in hemophiliacs with inhibitors. A follow-up trial is now being designed that will exclude chronically disabled joints and will allow a second "unknown" treatment and a longer period of observation.

**REFERENCES**


12. Lusher JM: Unpublished observations

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JM Lusher, PM Blatt, JA Penner, LM Aledort, PH Levine, GC White, AI Warrier and DA Whitehurst