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Intravenous Corticotrophin vs. Hydrocortisone in the Treatment of Hospitalized Patients with Crohn's Disease: A Randomized Double-Blind Study and Follow-Up

Alexander Chun, Ron M. Chadi, Burton I. Korelitz, Thomas Colonna, Joseph B. Felder, Mark H. Jackson, Eric H. Morgenstern, Steven D. Rubin, Andrea G. Sacknoff, and Gilbert M. Gleim

Sections of Gastroenterology and Medical Statistics, Department of Medicine, Lenox Hill Hospital and New York University School of Medicine, New York, New York, U.S.A.

Summary: Adrenocorticotrophic hormone (ACTH) and corticosteroids have no maintenance values for inflammatory bowel disease but serve to reduce the severity of disease. The effectiveness of intravenous corticotrophin versus hydrocortisone in ulcerative colitis has been determined including whether previous steroid therapy influenced the better response to one rather than the other, but no such studies have ever been done in Crohn's disease. Eighty-eight patients hospitalized with moderate-to-severe Crohn's disease (Present–Korelitz [P–K] Index –3 to –2 and the International Organisation for the Study of Inflammatory Bowel Disease–Crohn's & Colitis Foundation of America [IOIBD–CCFA] Index, mean 14, range 5–23) were treated in a prospective, randomized, double-blind clinical trial to receive either continuous intravenous infusion of 120 U/day of ACTH (44 patients) or hydrocortisone 300 mg/day (44 patients). Patients were also subdivided into those who received oral steroids during the 30 days prior to intravenous therapy and those who had not. Response was followed on a daily basis and tabulated at 3, 5, and 10 days. Patients were followed from 1–3 years to determine the later status. After 10 days of intravenous therapy 36 of 44 patients (82%) who received ACTH and 41 of 44 patients (93%) who received hydrocortisone fully responded (P–K index +3 and IOIBD–CCFA Index mean of 3). At the end of the study, response to intravenous ACTH and hydrocortisone was not statistically different whether or not patients received oral steroids during the 30 days prior to admission, although the response to IV ACTH tended to be faster at 3 days in those who had received previous steroid therapy. Intravenous ACTH and hydrocortisone are equally effective in achieving therapeutic goals in patients with Crohn's disease who have not achieved results with oral medications. Moreover the response rate was high (mean 88%), serving to buy time for establishment of successful maintenance programs of treatment with oral 5-ASA and immunosuppressive drugs for 69% of patients at 1–3 years. **Key Words:** Inflammatory bowel disease—Crohn's disease—Intravenous hydrocortisone—ACTH.

INTRODUCTION

The overall success of corticosteroid therapy in the treatment of ulcerative colitis has been well documented (1–3). Despite confirmation that corticosteroids have no maintenance value (2) and are responsible for both early and late complications (4,5), they serve to reverse the course of both chronic and deteriorating Crohn's disease just as they do in ulcerative colitis (6–10). Intravenous adrenocorticotrophic hormone (ACTH) and corticosteroids are also effective in Crohn's disease (11–12) and ulcerative colitis (10,12–18). They are still more effective than oral and intramuscular preparations used for ulcerative colitis (14,16), and this is also probably true for Crohn's disease. A major role for intravenous steroids has become the reduction of inflammation when Crohn's disease is deteriorating and thereby providing time for slower acting drugs like 5-ASA products and oral immunosuppressives, which do have maintenance value, to become effective. In treating hospitalized patients with ulcerative colitis, Meyers et al. (17) have shown that ACTH is more successful in reversing active disease when there has been no corticosteroid therapy during the 30 days before hospital admission, but intra-

Address reprint requests to Dr. B. I. Korelitz at Lenox Hill Hospital, 100 East 77th Street, New York, NY 10021-1883, U.S.A.
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venous hydrocortisone is more effective when the patient did receive steroids during the same period.

It is the purpose of this study to determine which of these two major categories of steroids accomplish remission more effectively in Crohn's disease and whether the presence or absence of previous steroids influences the choice in treatment as it has in ulcerative colitis.

METHODS

Eighty-eight patients consecutively admitted between 1990 and 1994 to the Inflammatory Bowel Disease (IBD) service at Lenox Hill Hospital with moderate-to-severe Crohn's disease (Present–Korelitz [P–K] Index –3 and –2 and International Organisation for the Study of Inflammatory Bowel Disease–Crohn's & Colitis Foundation of America [IOIBD–CCFA] Index, mean 14) were informed about the nature of this research study, enrolled, and signed the permission form approved by the Institutional Review Board. They were entered into a prospective, randomized, double-blind trial receiving either a continuous infusion of 120 units of ACTH in 1000 cc 5% dextrose in saline (44 patients) over 24 hours or hydrocortisone 300 mg over 24 hours daily (44 patients) in the same manner (Dose A). When the degree of hydration and depletion was improved the intravenous vehicle was changed to 0.5% normal saline and then to water, and the volume was reduced to 500 cc over 24 hours. In all instances the solution contained 20 mEq of potassium chloride. In the event of hypokalemia (potassium less than 3.5) the potassium was supplemented with runs of 10 mEq aliquots of KCl in 100 cc D5W over 1 hour.

The major goal of therapy was determined for each patient according to the P–K Index of Crohn's disease activity ranging from –3 to +3 established for 6-mercaptopurine (19). The patient was evaluated on a daily basis by two or more of the investigators for accomplishment of the determined goal. The index created by the IOIBD in conjunction with the CCFA was also logged each day (20–21). The results were tabulated for each patient on days 3, 5, and 10; lack of response at day 10, when the initial part of the study was terminated, was also recorded. If at day 3 or any day thereafter the improvement was progressive and obvious such as a +2 or +3 P–K Index or a 50% drop in the IOIBD–CCFA disease Index, the intravenous steroid drug was reduced to Dose B (80 units of ACTH or 200 mg hydrocortisone) and later to Dose C (40 units of ACTH or 100 mg hydrocortisone). If remission was fully attained at any intravenous dose level, open label oral prednisone was substituted at a dose of 40–60 mg per day and reduced thereafter.

After randomization to hydrocortisone or ACTH, patients were also subdivided in each group into those who had been receiving oral corticosteroids up until the time of hospital admission and those who had received no corticosteroids during the 30 days preceding admission. The oral steroid used prior to admission was prednisone. Only one patient used medrol 4 mg/day. The usual dose of prednisone ranged from 5 mg/day to 20 mg/day with a mean of 8 mg/day. The length of use of steroid varied fom 1 week to 2 years, most patients using it for less than 3 months prior to the study.

The sample size was determined to have a power of 0.80 to detect a 20% difference in the number of remissions at 10 days based on a remission rate of 80% in the hydrocortisone group, at an alpha level of 0.05. Chi-square analysis with Yates' correlation was used to determine differences in the proportion between the two groups. All analyses were based on intention to treat. Ninety-five percent confidence intervals were calculated according to the binomial theorem.

There was no gender bias because the sample had a total of 47 females and 41 males. The mean age was 36 years (33 for males and 39 for females) with an age range from 12–85 years. The distribution of Crohn's disease was similar in both groups (Table 1).

The extent of involvement could not always be ascertained at the time of randomization at admission but was always established before discharge.

RESULTS

The major goal of therapy (P–K Index) was determined at the time of randomization, and these are listed in Table 2. The goals were similar for the two groups. The goal in 59 of 88 (67%) patients was elimination of primary bowel symptoms, which included combinations

TABLE 1. *Distribution of Crohn's disease in 88 patients*

Site	ACTH no.	Hydrocortisone no.	Total patients no.
Gastric	1	0	1
Jejunoileitis	3	0	3
Ileitis and recurrent ileitis after surgery	18	18	36
Ileocolitis	7	4	11
Colitis	15	21	36
Recurrence in ileostomy	0	1	1
Total	44	44	88

The distribution of Crohn's disease was determined in some cases after randomization but before discharge.

TABLE 2. *Major goals of therapy*

	ACTH no.	Hydrocortisone no.	Total no.
Elimination of primary bowel symptoms	31	28	59
Reversal of small bowel obstruction	6	7	13
Reduction of abdominal mass	2	2	4
Heal fistula	0	3	3
Heal perirectal disease	3	2	5
Elimination of extra-intestinal manifestations	2	2	4
	44	44	88

of abdominal pain, diarrhea, fever, and malnutrition. The initial IOIBD–CCFA activity Index on admission was 5–23 (mean 14) for the whole group, 13 for patients on steroids prior to admission, and 15 for patients not on steroids.

The major goal of therapy was accomplished in 77 of 88 patients (90%, 95% CI, 79%–94%) within the 10-day period, including a 38% (CI, 28%–50%) response within 3 days and a 76% (CI, 68%–87%) response within 5 days (Table 3). The total response rate was high for both groups (82%, CI 67%–92% for ACTH vs. 93%, CI 84%–99% for hydrocortisone), and the number of patients who had achieved the goal of therapy at days 3, 5, and 10, or the cumulative total at day 10, was not significantly different for patients who received ACTH or hydrocortisone. The IOIBD–CCFA Index at that time ranged from 2–5 (mean 3) showing the effectiveness of therapy. The response to ACTH (vs. hydrocortisone) tended to be faster by day 3 in those who received steroids prior to admission than in those who had not (45% vs. 22%), but without statistical significance (Table 3), due to inadequate statistical power for this subset analysis.

Eleven of the 88 patients were not in remission after 10 days of intravenous ACTH or hydrocortisone. In only one instance did the patient warrant a bowel resection during the same admission (Table 4). One to three years' follow-up of all 88 patients entered into the study revealed that 24 patients (28%) eventually required surgery

TABLE 4. *Outcomes of 11 patients who failed to respond to intravenous ACTH or hydrocortisone by 10 days*

Well	1
Resection during same admission	1
Resection or ileostomy within 1–3 years	6
Chronically ill, no surgery	2
Died from other illness	1
Total	11

while 64 patients (72%) remained well on 5-ASA products or 6-mercaptopurine or combinations (Table 5). Of these 24 patients that eventually had surgery, 13 patients had been treated with ACTH and 11 with hydrocortisone. Two patients who responded fully to ACTH (P–K +3) developed uncomplicated adrenal hemorrhage on the day after intravenous therapy had been terminated. In both cases this condition resolved fully without complications.

DISCUSSION

The short-term role for oral corticosteroids has been secured for active ulcerative colitis (1–5) and for Crohn's disease (6–9). Early clinical experience seemed to support a similar role for intramuscular ACTH in ulcerative colitis (4,5,10,12,13,15) and again in Crohn's disease (6,7,11,12). The advantage of intensive intravenous therapy with corticosteroids in ulcerative colitis was later reported by Truelove and Jewell (14), Truelove et al. (16), and Jarnerot et al. (18).

The value of intravenous hydrocortisone vs. corticotrophin was first assessed in a controlled trial by Kaplan et al. for acute colitis in both diseases and they concluded that the two drugs were therapeutically equivalent (22). Later Meyers et al. (17) conducted a randomized double-blind trial of intravenous ACTH vs. hydrocortisone in 66 hospitalized patients with ulcerative colitis and concluded, as in the earlier study by Kaplan et al. (22), that ACTH was better when no oral steroids had been administered during the 30-day period before therapy, whereas hydrocortisone fared better if steroids were received dur-

TABLE 3. *Response to intravenous ACTH vs. hydrocortisone*

Goals* achieved by time: (day)	ACTH						Hydrocortisone					
	Previous steroids		No previous steroids		Total		Previous steroids		No previous steroids		Total	
	#	%	#	%	#	%	#	%	#	%	#	%
3	10	45%	11	50%	21	48%	4	22%	13	50%	17	39%
5	16	72%	15	68%	31	71%	12	66%	22	85%	34	78%
10	17	77%	19	87%	36	82%	15	83%	26	100%	41	93%

* Present-Korelitz Index +3

TABLE 5. *Outcomes of all 88 patients treated with intravenous ACTH or hydrocortisone within 3 years*

	No.	%
Additional admission for intravenous steroids	3	3
Well on maintenance drugs	61	69
Resection ± ileostomy	24	28
	88	100

ing the same period of time. Nevertheless only 42% of patients in that study had achieved overall remission (75% on ACTH and 22% on hydrocortisone) (17) and only 68% (22) and 72% (10) of patients in earlier studies.

Influenced by the experience of Zetzel and Atin (10), and Zetzel's observation of a rapid response to intravenous ACTH in both ulcerative colitis and Crohn's disease regardless of pretreatment with oral corticosteroid or not (12), this randomized controlled trial of hospitalized patients with Crohn's disease was undertaken because no similar controlled trial had been previously conducted specifically in this disease. The dose of 300 mg of hydrocortisone and 120 units of aqueous ACTH infused over 24 hr was chosen because these doses and methods of infusion had been used successfully by the senior author (B.I.K.) and had also been utilized by Meyers et al. (17) so that comparison could be made.

The overall combined favorable response of hospitalized patients with Crohn's disease to either intravenous hydrocortisone or ACTH was 90% at 10 days. This was in contrast to the 42% reported by Meyers et al. (17). While the difference might be explained by Crohn's disease vs. ulcerative colitis, by distribution of Crohn's disease, by the goals of therapy, and perhaps by different degrees of severity of the disease, 59 of 88 patients in the current study were admitted to the hospital for the management of primary bowel symptoms without specific complications, similar to the ulcerative colitis cases described by Meyers et al. (17). Furthermore, there had been no difference between hydrocortisone and ACTH in the overall response (41% and 44%, respectively) in the ulcerative colitis cases (17) vs. the Crohn's disease cases of the present study (93% and 82%). Nevertheless, a comparison of response between ulcerative colitis and Crohn's Disease was not a predetermined goal.

After 10 days of intravenous therapy in this study of Crohn's disease, 36 of 44 patients had fully responded to ACTH and 41 of 44 patients to hydrocortisone (P–K +3), verifying that they were equally effective in this setting. Only 11 of 88 patients had not reached the goals of therapy by 10 days (the later outcomes of these patients are shown in Tables 4 and 5). The difference in response to ACTH in patients who had previous steroids (77%) was less favorable but not significantly different from patients who had not received previous steroids (87%). Similarly, the difference in response to hydrocortisone in those who received previous steroids (83%) was less favorable than those who had not received previous steroids (100%) but again the difference was not statistically significant. This trend of equal response to ACTH and hydrocortisone was true in patients who had or had not received steroids earlier, after 5 days of therapy and after 10 days. At 3 days of therapy, however, the favorable response to ACTH in those who had previous steroids (45%) was twice as great as those responding to hydrocortisone (22%). This difference was not statistically significant. Nevertheless this more-rapid response to ACTH than hydrocortisone had been noted previously (14). Furthermore, we have noted a favorable response to ACTH after failure of hydrocortisone, an observation also made previously by others (12).

Long-term follow-up from 1–3 years after the study showed 28% of patients eventually required surgery whereas 72% remained well on 5-ASA products or 6-mercaptopurine or combinations. The total number of patients in the study that ended up requiring surgery was 24, and in 23 patients (96%) in this group surgery was elective. There was no significant difference in those ultimately requiring resection as to whether they had been earlier treated with ACTH or hydrocortisone. Of these 24 that eventually had surgery, 13 had been treated earlier with ACTH and 11 with hydrocortisone. Resection was performed 1–3 years after the intravenous steroid injection.

Hypokalemia occurred during intravenous therapy with both hydrocortisone and ACTH and was corrected by intravenous supplementation of potassium. There were no major complications of either form of therapy during the 10-day trial, with exception of adrenal hemorrhage occurring in two instances after ACTH. This complication has been reported elsewhere by us (23) and by others (24). In all cases the hemorrhage was unilateral and completely reversible. In both instances it occurred at or soon after the intravenous ACTH was terminated and oral corticosteroids were started.

We therefore conclude that intravenous hydrocortisone and ACTH are equally effective in achieving therapeutic goals in patients with Crohn's disease resistant to oral drug therapy regardless of whether they have received oral steroids in the 30 days prior to hospitalization. These results differ from those reported for ulcerative colitis.

We have additionally observed that the response in this study of either type of intravenous steroid can be long lasting (72%). Intravenous steroids should be used more often than oral steroids to buy time, thereby pro-

viding an opportunity for maintenance therapy, including 5-ASA products, 6-mercaptopurine, or combinations, to be effective.

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