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Bolus administration of steroid therapy is more favorable than the conventional use in preventing decrease of bone density and the increase of body fat percentage in patients with inflammatory bowel disease☆

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Abstract

Introduction: The effects of short course of corticosteroids on the metabolic processes and bone formation has not been well studied. Our aim was to compare the efficacy, the side effects and the bone and lipid metabolisms in IBD patients using bolus or conventional tapering of methylprednisolone for 12 weeks.
Patients and methods: Nineteen IBD patients received intravenous methylprednisolone of 1 mg/kg for 5 days tapered by 4 mg per week. Patients were prospectively randomized in two groups. In "conventional" group (I) steroids were given daily. In "pulse" group (II) weekly doses of steroids were given on special days of the week. The body mass index (BMI) was measured before and after the corticosteroid therapy. Blood samples were collected to assess glucose level, electrolytes, cholesterol and triglyceride levels, inflammatory parameters, cortisol, osteocalcin and crosslaps values. Total body composition analysis was performed at the beginning and at the end of the steroid therapy.

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Results: In Group I, BMI increased, total body bone density decreased significantly at the end of the steroid therapy. Body fat percent showed a tendency to be higher at the end of steroid therapy in Group I. Cholesterol level increased significantly in Group I patients. The decrease in serum cortisol level was more remarkable in Group I vs. Group II after steroid therapy. Less side-effect occurred in Group II vs. Group I.
Discussion: Our results suggest that bolus tapering of corticosteroids may have more favorable short term outcome than conventional tapering that may revolutionize steroid therapy in IBD.

1. Introduction

Corticosteroids still have an important role in the management of acute episodes of inflammatory bowel disease (IBD-Crohn's disease [CD], ulcerative colitis [UC]). Parenteral corticosteroids are usually the first treatment of choice for hospitalized patients with severe UC and CD.[1] However, use of steroids is associated with some well-known potential harmful side-effects; therefore oral steroids are recommended to be gradually tapered off and discontinued after 12 weeks in case of appropriate response to the parenteral therapy. Corticosteroid therapy is known to contribute to changes in body composition with the alteration of protein synthesis and degradation in skeletal muscle, resulting in decreased muscle mass and reduced fat-free mass. Steroids also lead to a reduction in the total body bone mineral density (BMD).[2] Therefore total body composition analysis is a useful method for quantification of multiple whole body and regional components, including bone mineral, fat, and lean soft tissue in patients treated with steroids. It gives a direct measurement of the percent body fat, muscle and bone (in grams) for the entire body and sub regions like the arm, leg, and trunk.

The optimal dose response for parenteral steroids in the treatment of severe attacks has not been clarified yet; dosages of methylprednisolone 40–60 mg or 1 mg/kg per day orally are the most frequently used regimen[1,3] for flare up. Furthermore, no randomized trials have studied and even no guidelines have been developed by the European Crohn's and Colitis Organisation on taper schedules. After the induction of remission, methylprednisolone is usually tapered 8–16 mg weekly until a daily dose of 32 mg is reached followed by a tapering of 4 mg/week. Tapering steroid regimen is most frequently carried out by administrating the drug daily, although alternate-day steroid management (given every other day) has also been a widely employed and effective mode of therapy for ages associating with fewer unpleasant side effects.[4] The efficacy of "bolus-administered" corticosteroids when weekly dose of steroid regimen is given on special days has not been previously examined in patients with IBD. The effect of a "short-term" 12-week course of corticosteroids on the metabolic processes and bone formation has not been well studied too; although these are some of the most important side effects should be considered.

The aim of the present pilot study was to compare the efficacy, the frequency of side effects and the changes in bone and lipid metabolism in IBD patients using bolus or conventional tapering of methylprednisolone for 12 weeks.

2. Patients and methods

2.1. Study design and patients

This single-center, prospective, randomized trial was carried out from November 2011 to February 2013 on consecutive patients with acute exacerbation of IBD and not being on steroid therapy admitted to our clinic. Diagnosis was based on the Lennard-Jones criteria.[5] Crohn's disease phenotype was determined according to the Montreal classification.[6] Clinical activities were determined by Crohn's Disease Activity Index (CDAI)[7] in CD and by partial Mayo score[8] in UC. Twenty patients were enrolled in the study. The median CDAI and partial Mayo score were 184 and 6 in CD and UC at the time of the enrolment. None of the patients received oral corticosteroid at the time or at least 6 months before the enrolment. On admission a complete blood chemistry including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum glucose, electrolytes, liver and renal function, cholesterol, triglycerides, blood count, serum cortisol, calcium, dehydroepiandrosterone (DHEA), thyroid stimulating hormone (TSH), parathyroid hormone (PTH), β-crosslaps and osteocalcin levels were performed before starting steroid therapy. The mean value of CRP, ESR, leukocytes and thrombocytes before steroid therapy were 16 mg/l, 21.5 mm/h, 8.828 G/l and 322 G/l. Flexible colonoscopy or sigmoidoscopy with biopsies was carried out only in patient with relevance to therapy, however, it was not essential for inclusion into the trial. Thus, 3 CD and 13 UC patients underwent colonoscopy at inclusion. DXA total body composition analysis was also performed at the beginning of the study to determine the fat and fat-free component of the body.

Patients eligible for iv. steroid therapy received methylprednisolone dosage 1 mg/kg for 5 days. After iv. therapy, patients were prospectively randomized in two groups. In "conventional" group (Group I) methylprednisolone was given daily while in "bolus-administered" group (Group II) weekly dose of steroids was given on special days of the week. 64 mg/day methylprednisolone dose at the first week in Group I was equal to 150 mg/day given in the first 3 days in Group II. Finally, both groups received the same methylprednisolone dose and it was tapered by 4 mg per week in both groups. The two different types of methylprednisolone dosages are detailed in Table 1. Follow-up appointments were done every two weeks. These visits involved the assessment of the clinical activities by the determination of CDAI and pMayo scores. Patients were asked about side effects, the body mass index was determined and the waist and hip circumferences were also measured. Laboratory assessment

Table 1 Methylprednisolone dosages in the conventional and the bolus administration groups.

Week/day	1	2	3	4	5	6	7	Total dose
Conventional administration								
1	64	64	64	64	64	64	64	448
2	48	48	48	48	48	48	48	336
3	32	32	32	32	32	32	32	224
4	28	28	28	28	28	28	28	196
5	24	24	24	24	24	24	24	168
6	20	20	20	20	20	20	20	140
7	16	16	16	16	16	16	16	112
8	12	12	12	12	12	12	12	84
9	8	8	8	8	8	8	8	56
10	4	4	4	4	4	4	4	28
11	2	2	2	2	2	2	2	14
12	0	0	0	0	0	0	0	0
Bolus administration								
1	150	0	150	0	150	0	0	450
2	112	0	112	0	112	0	0	336
3	75	0	75	0	75	0	0	225
4	98	0	98	0	0	0	0	196
5	84	0	84	0	0	0	0	168
6	70	0	70	0	0	0	0	140
7	112	0	0	0	0	0	0	112
8	84	0	0	0	0	0	0	84
9	56	0	0	0	0	0	0	56
10	28	0	0	0	0	0	0	28
11	12	0	0	0	0	0	0	12
12	0	0	0	0	0	0	0	0

(including inflammatory parameters, electrolytes, glucose level, liver and renal function, and blood count) was carried out every four weeks. Detailed laboratory parameters (DHEA, TSH, PTH, serum cortisol, serum β-crosslaps and osteocalcin levels) and DXA for total body composition analysis were performed at week 0 and week 12. Clinical remission was defined as a CDAI of <150 points and a Mayo score of <2 points. The study was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee of the University of Szeged (Number: 74/2011).

2.2. End points

The primary end point of the study was the comparison of the efficacy of the conventional and the bolus-administered corticosteroid therapy and also the assessment of their effects on the adrenal glands hormone secretion and on the lipid and bone metabolisms. Secondary end points were the frequency of steroid-related side effects in the two groups.

2.3. Statistical analysis

Student's *t*-test was employed to compare continuous variables. Multivariate analysis with stepwise logistic regression by SPSS software was performed to investigate the parameters with a possible influence on clinical outcome, such as age, gender, location of disease, duration of disease, concomitant immunosuppressive therapy. The differences between the two groups were performed by mixed effects ANOVA model for repeated measures. The results were corrected using a Bonferroni–Holm method for multiple testing. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics, clinical response

During the study period, 20 patients with IBD (5 with CD, 15 with UC) were enrolled. At day 5, all but one patient achieved clinical remission. One patient proved to be refractory to intravenous steroid and needed rescue therapy therefore she was excluded because of treatment failure. Methylprednisolone was tapered weekly and stopped at week 12 in these 19 patients who could complete the study. The clinical characteristics of the participated 19 patients are presented in Table 2. Ten patients had already been diagnosed with IBD, while the remaining 9 patients were at disease onset. Although the male/female ratio was higher in Group II, baseline clinical characteristics of patients did not differ significantly between the two treatment groups. CDAI and pMayo score showed decreasing pattern in both groups during the steroid therapy. CDAI and pMayo score decreased to a median value of 21 and 0 (median CDAI 35, median partial Mayo score 0 in Group I and 12 and 0 in Group II) at the end of the steroid therapy. Median CDAI and pMayo scores during the "conventional" and the "bolus" methylprednisolone treatment periods are indicated in Table 3. The mean values of CRP, ESR, leukocytes and thrombocytes after steroid therapy were 7.4 mg/l, 9.7 mm/h, 7.935 G/l and 238 G/l. The effects of bolus therapy on the clinical and laboratory parameters of disease activity did not differ from the conventional administration. The patients in both groups had not relapsed at the discontinuation of steroid therapy.

Table 2 Clinical characteristics of the enrolled patients.

	Group I (n = 9)	Group II (n = 10)
Mean age at the diagnosis (years)	34.3	30.3
Mean disease duration (years)	5.2	6.2
CD/UC	3/6	3/7
Female/male	4/5	2/8
Location/extension		
– Ileal	1	2
– Colonic	2	1
– Ileocolonic	–	–
– Extensive colitis	3	5
– Left-sided colitis	3	2
– Proctitis	–	–
Concomitant therapy		
– 5-ASA	4	6
– Budesonide	0	2
– Azathioprine	3	4
– Metronidazole	2	1

Table 3 Median CDAI and pMayo scores during the "conventional" and the "bolus" methylprednisolone treatment periods.

Weeks	Group I		Group II	
	Median CDAI	Median pMayo	Median CDAI	Median pMayo
0	204	6.2	164	5.1
2	184	5	152	4
4	146	3.4	126	2
6	86	1	90	0
8	72	0	64	0
10	68	0	48	0
12	35	0	12	0

3.2. Changes in adrenal glands hormone secretion, in the lipid and bone metabolism after methylprednisolone therapy

In Group I, BMI increased significantly at the end of the steroid therapy ($p = 0.008$). In Group II, no difference was observed in BMI before and after the steroid therapy. Total body composition analysis showed significant decrease in bone density in Group I ($p = 0.032$). Body fat percent showed a tendency to be higher at the end of steroid therapy in Group I, although the difference was not significant.

Considering the laboratory parameters, serum cholesterol level increased significantly in Group I patients after steroid therapy ($p = 0.028$). The decrease in serum cortisol level was more remarkable in Group I vs. Group II after steroid therapy ($p = 0.02$ and $p = 0.055$). Fig. 1 summarizes the significant changes in the examined parameters.

No changes were detected in the waist and hip circumference, T and Z scores, electrolytes, liver and renal function, serum glucose, serum calcium, triglyceride, DHEA, TSH, PTH and β-crosslaps before and after the steroid therapy neither in Group I, nor in Group II.

3.3. Steroid-related side effects

The most common side effects occurring during the therapy were the Cushingoid appearance, development of acne, fatigue, gastrointestinal complaints. Side effects were presented in 5/9 (55.6%) vs. 4/10 (40%) of the patient in Groups I and II. Cushingoid appearance did not occur in Group II. The side effects are summarized in Table 4.

4. Discussion

This prospective study revealed that "bolus-administered" corticosteroid therapy was as effective as the conventional administration of the drug, but had less harmful effects on bone and lipid metabolims and was associated with fewer side effects than the previous one. Significant increase in BMI and serum cholesterol level and decrease in body density were shown when methylprednisolone was tapered conventionally, compared to the bolus administration of the drug. Body fat percent also showed a tendency to be higher at the end of steroid therapy in patients using the conventional tapering regimens. Cushingoid appearance also occurred only in patients on conventional administration.

For the past 30 years, corticosteroids have been the mainstay of therapy in patients with moderate to severe active IBD.[9] Intravenous therapy generally produces rapid improvement of symptoms. Once improvement has been achieved, corticosteroids should be tapered gradually per week until the drug is discontinued. The mean goal of IBD therapy is to decrease the steroid-related side-effects and to minimize steroid dependency with the development of new series of anti-inflammatory glucocorticoids with

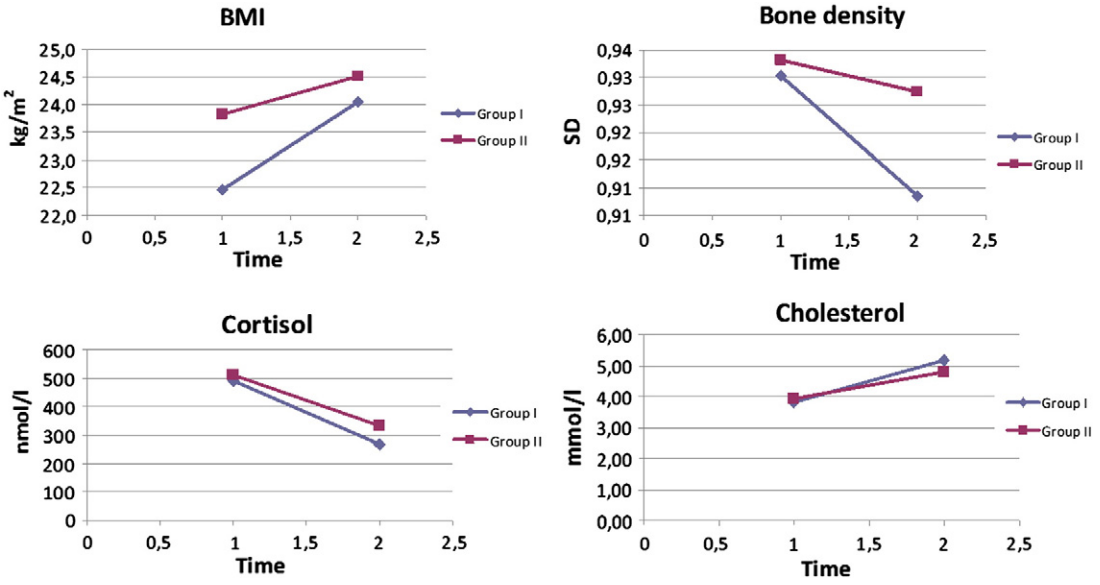

Figure 1 Significant changes in the examined parameters after 12-week methylprednisolone therapy in Groups I and II.

Table 4 Side effects developed in patients in Groups I and II.

Patients	Side effects
Group I	
Patient 1	Cushingoid appearance
Patient 2	Cushingoid appearance
Patient 3	Acnes
Patient 4	Acnes
	Arthralgia
Patient 5	Cushingoid appearance
	Arthralgia
	Fatigue
	Nausea
	Stomatitis
Group II	
Patient 1	Acnes
Patient 2	Acnes
Patient 3	Arthralgia
Patient 4	Fatigue
	Hypertension

enhanced topical potency and less systemic activity such as budesonide or beclamethasone.[10] Less attention is paid to the dosing of steroids, although it seems to be also important.

Although there are no trials between different steroid-tapering regimens, the goal in the daily practice is to get patients off corticosteroids within 12 weeks and maintain disease remission. Alternatively, alternate-day corticosteroid therapy can also be used in patients with refractory Crohn's disease — even for longer time.[11] However, some available evidence suggested that the manner of corticosteroid tapering probably did not change the long term outcome in IBD.[12] Use of "bolus-administered" steroids is a novel possibility to optimize the therapy. Bolus administration is actually an untested manner that has been anecdotally recognized to be more effective than the conventional use of steroid therapy. Multiple doses of steroids were previously shown to cause more adverse effects than a single dose.[13] In a single-center, double-blind trial performed by Bossa et al., patients with a severe attack of UC were scheduled to receive equal iv. doses of methylprednisolone, randomly given as either a bolus injection administered twice daily or continuous infusion.[14] Methylprednisolone given as a continuous infusion was no better than bolus administration in terms of efficacy and safety. The aim of bolus steroid therapy is to get quicker and stronger anti-inflammatory effect. Giving a higher dose of methylprednisolone, an immediate profound anti-inflammatory effect is supposed to be achieved with lower toxicities and no prolonged suppressive effect on the hypothalamic–pituitary axis.

Our results did not show any significant difference according to the disease outcome between the two administration types at the end of the therapy and at follow up times for any of the clinical or laboratory parameters measured, confirming the same efficacy of bolus therapy as in case of conventional administration.

The widespread use of corticosteroids has been associated with an increased incidence of a variety of adverse effects involving the musculoskeletal, the endocrine, the metabolic system, the neuropsychiatric wellbeing, the GI system, the skin, the eyes, the infectious risk, the cardiovascular and the hematological system.[12] Dosage and duration of therapy are some of the most important factors influencing the development of the toxic effects of corticosteroids. Although no data is available on the harmful effects of short term corticosteroid therapy on lipid and bone metabolism, our results revealed that short-term use of steroids increases BMI and body fat percent and decrease bone density. Common adverse effects of short term therapy include moon face, mood changes, insomnia, GI intolerance, weakness, fluid retention, weight gain, increased appetite, increased infections, amenorrhea, elevated blood glucose, slow wound healing, striae, and acneiform rash. Alternate-day steroid therapy may decrease hypothalamic–pituitary–adrenal axis suppression and therefore the development of certain side effects.[15] However, in this study, the most common side effects occurred more frequently in patients with conventional vs. bolus-administration steroid therapy.

Osteoporosis is present in 30–45% of patients with CD, and its rate is somewhat lower in patients with UC.[15,16] Osteopenia is likely related to the chronic inflammatory process itself, and furthermore triggered by steroid use. Steroid related osteoporosis is multifactorial; decreased calcium absorption, development of secondary hyperparathyroidism, stimulating osteoclast activity, and decrease osteoblast production are only some of the potential etiological factors.[17] Hyperlipidemia is also a common side effect of steroid therapy.[18] Steroids are supposed to influence lipid metabolism by redistributing body fat and facilitating of effects of lipolytic agents. Large doses of glucocorticoids lead to redistribution of fat to the upper trunk and face, with a concomitant loss of fat in the extremities.[19] Our result revealed beneficial effect of bolus-administered corticosteroid therapy on bone density and body fat percent.

The main limitation of this pilot study is the low number of participating patients. This is mainly due to the relatively high costs of total body composition analysis, which is used for the accurate determination of the various body weight components: fat mass, fat-free mass, total body water and bone mass.[20] However, use of total body composition analysis gives a valuable part of this prospective randomized study, since the alterations of bone and lipid metabolisms could be examined in a parallel way.

In conclusion, this single-center study suggests that bolus tapering of equivalent doses of methylprednisolone administered in conventional daily doses has equivalent clinical efficacy, but more favorable side effect profile. As no significant difference was detected between the two administration types on the clinical and laboratory parameters of disease activity, it appears that bolus administration of corticosteroids can safely and effectively replace the conventional use of methylprednisolone for active IBD. Of course, further controlled, randomized trials are needed to confirm these results that may revolutionize steroid therapy in IBD.

Conflict of interest

The authors have declared that they have no conflict of interest.

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