Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis

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Authors' objectives

To examine the role of rectal corticosteroids in the management of active ulcerative colitis.

Searching

MEDLINE was searched from 1966 to 1996 and EMBASE from 1985 to 1996 using the MeSH terms 'inflammatory bowel disease', 'therapy', and 'topical administration', 'enema' or 'suppository'. Bibliographies of all relevant studies were scanned.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) of rectal steroids in the treatment of active ulcerative colitis were included if a symptom score was one of the main outcomes and the minimum duration of treatment was 2 weeks. The duration of treatment in the primary studies ranged from 14 to 56 days.

Specific interventions included in the review

Rectal corticosteroids including hydrocortisone, prednisolone, betamethasone, budesonide, methylprednisolone, prednisolone metasulphobenzoate and beclomethasone were studied.

Comparison treatments included rectal aminosalicylates (4-ASA and 5-ASA), oral corticosteroids, placebo and rectal budesonide. Rectal preparations included suppositories, foam and liquid enemas.

Participants included in the review

Patients were included if they had active ulcerative colitis with a documented disease margin distal to the splenic flexure on radiographic studies or less than 60 cms from the anal verge at flexible sigmoidoscopy or colonoscopy.

Outcomes assessed in the review

The proportion of patients that improved or attained remission or both by symptomatic, endoscopic and histological criteria was the outcome assessed. Provided that an adequate definition of improvement or remission was offered, the authors' criteria for these outcomes was accepted.

How were decisions on the relevance of primary studies made?

Two independent observers assessed each retrieved study according to pre-determined inclusion criteria.

Assessment of study quality

A 30-point scoring system was used to assess validity. No further details are given. Two observers scored each study and disagreements were settled by consensus.

Data extraction

The following data were extracted using a pre-defined format: number of patients enrolled, number completing the study, sex, disease distribution, dose, frequency, duration and formulation of treatments and adverse effects of therapy. An intention-to-treat principle was adopted in the data extraction. The number of observers carrying out the data extraction was not stated.

Methods of synthesis

How were the studies combined?
The common odds ratio (OR) was calculated along with the 95% confidence interval for each group according to Mantel-Haenszel and using the method of DerSimonian and Laird. Continuous data points were pooled and compared using a weighted mean difference. Overall response rates for each drug were calculated by dividing the total number of patients reaching an end point by the total number of patients treated.

**How were differences between studies investigated?**

Homogeneity within groups of trials was confirmed using the Breslow-Day test.

**Results of the review**

33 RCTs were used to assess the role of rectal corticosteroids (N = 2406 patients).

2 RCTs were used to compare rectal corticosteroids and placebo (N = 58 patients).

2 RCTs were used to compare rectal budesonide and placebo (N = 274 patients).

2 RCTs were used to compare rectal and oral corticosteroids (N = 96 patients).

7 RCTs were used to compare rectal corticosteroids and rectal 5-ASA (N = 682 patients).

2 RCTs were used to compare rectal corticosteroids and rectal 4-ASA (N = 85 patients).

5 RCTs were used to compare rectal corticosteroids and rectal budesonide (N = 463 patients).

3 RCTs were used to compare mean cortisol concentrations after 4 weeks of treatment with rectal budesonide compared to conventional rectal corticosteroids (N = 224 patients).

Median validity score (out of 30) was 21 (range 9 to 26). Adverse effects were inconsistently reported.

Conventional rectal corticosteroids (hydrocortisone, prednisolone, betamethasone): improvement rates: symptomatic 77%, endoscopic 66%, histological 52%; remission rates: symptomatic 45%, endoscopic 34%, histological 30%.

Topically active corticosteroids (budesonide, beclomethasone, prednisolone meta sulphobenzoate): improvement rates: symptomatic 73%, endoscopic 69%, histological 55%; remission rates: symptomatic 46%, endoscopic 31%, histological 23%.

Aminosalicylates (5-ASA or 4-ASA): improvement rates: symptomatic 81%, endoscopic 75%, histological 65%; remission rates: symptomatic 52%, endoscopic 39%, histological 32%.

Placebo: improvement rates: symptomatic 34%, endoscopic 38%; remission rates: symptomatic 9%, endoscopic 17%.

Rectal corticosteroids and placebo: improvement: symptomatic OR = 0.21 (95%CI: 0.07, 0.71), endoscopic OR = 0.27 (95%CI: 0.10, 0.77); remission: symptomatic OR = 0.07 (95%CI: 0.02, 0.29), endoscopic OR = 0.34 (95%CI: 0.10, 1.20).

Rectal and oral corticosteroids: could not be pooled due to substantial differences in oral dose.

Rectal corticosteroids and rectal 5-ASA: improvement: symptomatic OR = 1.36 (95%CI: 0.88, 2.09), endoscopic OR = 1.06 (95%CI: 0.61, 1.85), histological OR = 2.27 (95%CI: 1.22, 4.27); remission: symptomatic OR = 2.42 (95%CI: 1.72, 3.41), endoscopic OR = 1.89 (95%CI: 1.29, 2.76), histological OR = 2.03 (95%CI: 1.28, 3.20).

Analysis repeated after excluding a trial with larger volume of 5-ASA and after excluding trials using foam preparations: 5-ASA remained superior (no results given).

Rectal corticosteroids and rectal 4-ASA: improvement: symptomatic OR = 3.88 (95%CI: 1.29, 11.64).

Rectal corticosteroids and rectal budesonide: improvement: symptomatic OR = 2.08 (95%CI: 0.84, 5.14), endoscopic
OR = 1.40 (95%CI: 0.87, 2.25), histological OR = 1.23 (95%CI: 0.80, 1.91); remission: symptomatic OR = 0.85 (95%CI: 0.44, 1.63), endoscopic OR = 1.14 (95%CI: 0.69, 1.88), histological OR = 0.68(95%CI: 0.28, 1.67).

Rectal budesonide and rectal 5-ASA: endoscopic OR = 0.58 (95%CI: 0.27, 1.22); remission: one OR and CI reported but it is not clear which outcome is referred to.

Mean cortisol concentrations after 4 weeks of treatment with rectal budesonide compared to conventional rectal corticosteroids: weighted mean difference between pooled treatment arms = 119.1 nmol/l (95%CI: 70.3, 167.9).

Cost information
Unit cost per medication and cost of 14 days treatment is reported in Canadian and USA dollars and UK pounds.

Authors' conclusions
Rectal 5-ASA is superior to rectal corticosteroids in the management of active distal ulcerative colitis.

CRD commentary
This review includes details of the methods used to select studies for inclusion, scoring of scientific rigour of the primary studies and data extraction. Reasons are stated for the exclusion of some retrieved trials. Data were extracted on an intention-to-treat basis. It is not stated whether the literature search was limited to articles in a specified language. Although it is stated that the primary studies were scored for validity, and a 30-point scoring system was used, no further details of the criteria used to assess validity are given and no further information is given in the article referenced. Fuller details of the included studies, such as the characteristics of the participants and baseline comparability of treatment groups, would have been welcome. The authors used the original definitions of "improvement" and "remissions" but no details are given of these definitions and there is no assessment of the comparability of the definitions used among trials. Homogeneity was statistically tested but no results are given. The authors mention the inconsistent reporting of adverse reactions, and without an assessment of adverse reactions, no evaluation of therapy is complete. Without fuller details of the primary studies and evaluation of the validity, it is not possible to support the authors conclusion on the evidence offered.

Implications of the review for practice and research
The review could be repeated with fuller details of the included studies and containing a full evaluation of the validity of the primary studies.

Bibliographic details

PubMedID
9245932

Original Paper URL
http://gut.bmjournals.com/cgi/reprint/40/6/775

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM
MeSH
Administration, Oral; Administration, Rectal; Aminosalicylic Acids /therapeutic use; Anti-Inflammatory Agents /adverse effects /therapeutic use; Anti-Inflammatory Agents, Non-Steroidal /therapeutic use; Budesonide; Colitis, Ulcerative /drug therapy; Glucocorticoids /therapeutic use; Humans; Mesalamine; Pregnenediones /therapeutic use; Randomized Controlled Trials as Topic; Suppositories

AccessionNumber
11997000863

Date bibliographic record published
30/11/1998

Date abstract record published
30/11/1998

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.