

## Use of the ‘nutriceutical’, bovine colostrum, for the treatment of distal colitis: results from an initial study

Z. KHAN\*, C. MACDONALD\*, A. C. WICKS\*, M. P. HOLT†, D. FLOYD\*, S. GHOSH‡, N. A. WRIGHT‡ & R. J. PLAYFORD‡

\*Department of Gastroenterology, Leicester General Hospital, Leicester, UK; †Medical Statistics, South Derbyshire Acute Hospitals NHS Trust, Derbyshire, UK; ‡Imperial College Faculty of Medicine, Hammersmith Hospital Campus, London, UK

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### SUMMARY

**Background:** Bovine colostrum is a rich source of nutrients, antibodies and growth factors.

**Aim:** To examine the efficacy of colostrum enemas in the treatment of distal colitis using a randomized, double-blind, controlled protocol.

**Methods:** Fourteen patients (eight female), with a mean age of 45 years (range, 16–75 years) and mild to moderately severe distal colitis (Powell-Tuck scoring system), received colostrum enema (100 mL of 10% solution) or placebo (albumin solution) b.d. for 4 weeks. Both groups also received mesalazine (1.6 g/day) or, if already taking it, had a dose increment of 1.6 g/day. Disease activity was documented at 0, 2 and 4 weeks.

**Results:** After 4 weeks, the colostrum group showed a mean reduction in symptom score of  $-2.9$  (95% confidence interval (CI),  $-5.4$  to  $-0.3$ ), whereas the placebo group showed a mean response of  $+0.5$  (95% CI,  $-2.4$  to  $+3.4$ ). The histological score improved in five of the eight patients in the colostrum group (mean response,  $-0.9$ ; 95% CI,  $-1.69$  to  $-0.03$ ), whereas the histological scores only improved in two of the six patients in the placebo group (mean response,  $0.2$ ; 95% CI,  $-2.4$  to  $+2.6$ ).

**Conclusions:** Bovine colostrum enema shows potential as a novel therapy for left-sided colitis with additional benefits over using mesalazine alone. Further studies appear to be warranted.

### INTRODUCTION

Ulcerative colitis is a severe relapsing disease of unknown aetiology in which patients usually present with increased bowel frequency with the passage of mucus and/or blood. Current therapeutic strategies usually involve the use of 5-aminosalicylic acid derivatives. These drugs are effective in inducing remission in about 30–40% of patients after 4 weeks of therapy, rising to about 60–70% after 8–12 weeks of treatment.<sup>1</sup> The value of increasing the 5-aminosalicylic acid dosage

in patients who relapse and who are already receiving maintenance therapy is, however, less clear. Alternative therapies mainly involve the use of powerful immunosuppressants, such as prednisolone, with its associated side-effects: development of cushingoid features, glucose sensitivity and osteoporosis. Novel approaches are therefore required.

Colostrum is the first milk produced after birth and is particularly rich in immunoglobulins, antimicrobial peptides (e.g. lactoferrin, lactoperoxidase) and other bioactive molecules, including growth factors.<sup>2</sup> In combination with the milk that is subsequently produced, it is important for the nutrition, growth and development of the new-born infant, and contributes to the immunological defence of the neonate. Some studies

Correspondence to: Professor R. J. Playford, Gastroenterology Section, Imperial College School of Medicine, Hammersmith Hospital Campus, DuCane Road, London W12 0NN, UK.  
E-mail: r.playford@ic.ac.uk

suggest that it may be of value in eliminating infection and stimulating growth of the neonatal gastrointestinal tract.<sup>3, 4</sup> Its value in the prevention and treatment of adult gastrointestinal injury is, however, largely unexplored. We have shown recently, using a combination of *in vitro* and *in vivo* studies, that a commercially available defatted bovine colostrum preparation can reduce non-steroidal anti-inflammatory drug (NSAID)-induced upper intestinal gut injury in rats, mice and humans.<sup>5, 6</sup> However, as proton pump inhibitors are efficient in reducing gastric damage, the major clinical value of such products is likely to be in the prevention or reduction of injury to the bowel for conditions distal to the stomach, such as inflammatory bowel disease.<sup>2</sup> We have therefore extended our studies to examine the clinical value of bovine colostrum enemas for patients with colitis restricted to the left side of the colon.

## METHODS

### *Preparation of colostrum and control solutions*

The colostrum solution was identical to that used in the previously published *in vitro* and *in vivo* studies,<sup>5, 6</sup> and was prepared by Viable Bioproducts, Turku, Finland. The initial colostrum solution was passed through a microfilter (0.2 mm pore), and the final colostrum whey solution ('Bioenergi') is free of fat (including polar lipids) and lactose, and is reduced in most of the major milk proteins, including casein and lactalbumin, with the remaining protein being relatively rich in immunoglobulins and growth factors. The total protein content of the colostrum solution was 4.3 mg/mL. The concentrations of the various growth factors present in the colostrum preparation are incompletely defined, but include: insulin-like growth factors-I and -II, each at about 2 mg/L, transforming growth factor- $\alpha$  at 25  $\mu$ g/L and epidermal growth factor at 6  $\mu$ g/L (data supplied by SHS International Ltd, personal communication, 1999). The control solution, made up from bovine serum albumin, provided an iso-proteinaceous solution that had a similar appearance to the colostrum preparation, but was free of growth factor constituents.

### *Study protocol and ethical approval*

Local ethical approval was obtained and all patients gave informed written consent. Subjects were recruited from patients being reviewed at the Out-patient

Department of the University Hospitals Leicester with active colitis. Entry criteria necessitated that the patients should have had a worsening of symptoms that required additional therapy, and a disease severity of  $\geq 5$  on the St Marks system was needed.<sup>7</sup> In addition, histological confirmation of the diagnosis was required in all cases. None of the patients had taken steroid therapy, azathioprine or any other immune modulatory drug for at least 2 months prior to the trial.

Patients were excluded from the study if the severity of illness was sufficient to require in-patient hospital admission or intravenous steroids, or if the disease extent was limited to the rectum (i.e. proctitis) or extended proximal to the left colon (i.e. beyond the splenic flexure at fiberoptic endoscopy).

Patients attended the clinic on three occasions (0, 2 and 4 weeks). At each consultation, a clinical history and examination were undertaken and blood was taken for haemoglobin, white cell count, platelets, albumin and C-reactive protein. On the initial visit, all patients underwent a fiberoptic colonic examination to 50 cm (splenic flexure). At subsequent visits, a rigid sigmoidoscopy with biopsies was performed. Biopsies were taken from the midpoint of the diseased area and at the same place at subsequent assessments.

At the initial visit, patients were shown how to administer an enema and were randomized to receive enemas containing either the colostrum preparation (100 mL, 10% solution) or control solution, twice daily for 4 weeks. Patients in both arms of the trial were also given mesalazine at a dose of 1.6 g/day or, if already taking mesalazine, the dose was increased by a further 1.6 g. At each visit, compliance with medication was checked. Neither the patient nor the investigators were aware of which of the two arms the patients were entered into. A final review of the clinical notes was performed 6 months after instigation of therapy to document any clinical relapse requiring steroid therapy.

### *Symptom scoring*

Detailed questioning of bowel symptoms was elicited to allow a symptom score, based on the 'Powell-Tuck' system, to be determined.<sup>7</sup> This well-validated scoring system is based on an assessment of 'patient well-being' (0–3), abdominal pain (0–2), rectal bleeding (0–3), temperature (0–2), anorexia/nausea (0–1), bowel frequency (0–3), stool consistency (0–2), abdominal tenderness (0–3) and the presence of extra-intestinal

manifestations (0–1). All patients were required to have a minimum Powell-Tuck score of five to qualify for entry into the study.

*Sigmoidoscopic examination and scoring*

The degree of injury seen on sigmoidoscopic examination was given a score of 0–3, based on the scale suggested by Baron *et al.*, where 0 = normal, 1 = loss of vascular pattern, 2 = contact bleeding and 3 = spontaneous bleeding.<sup>8</sup> Patients were required to have a minimum Baron score of two to be included in the study.

*Histological scoring*

Biopsies were fixed in formalin, sectioned and stained with haematoxylin and eosin. They were graded on a score of 0–3 by a blind observer according to the method of Truelove and Richards.<sup>9</sup> 0 = normal lamina propria cellularity or minor increase in chronic inflammatory cell content; 1 = definite chronic inflammatory infiltrate in the lamina propria with basal plasma cells; minimal acute inflammation; 2 = definite chronic inflammatory infiltrate with conspicuous acute inflammatory infiltrate in the lamina propria; at most, occasional neutrophil polymorphs in the crypt epithelium; 3 = lamina propria as for 2, but with prominent cryptitis and/or crypt abscess formation. Patients were required to have a minimum score of one to be included in the study.

*Study end-points*

End-points were significant improvements in the patient’s symptom score, mucosal appearance on sigmoidoscopy and histological score of mucosal biopsies (assessed by a single blind individual, NAW) after 2 and 4 weeks of enema therapy.

*Statistics*

Disease activity (Powell-Tuck) scores are expressed as the group mean ± S.E.M. Sigmoidoscopy and histology assessment are presented as the median (interquartile range). Changes in the Powell-Tuck, sigmoidoscopic and histological scores are expressed as the mean (95% confidence interval (CI)) for change. Comparisons within groups, across time, were analysed on a paired

basis. Data were analysed using the SAS statistical package and *P* < 0.05 was taken as the level of significance.

**RESULTS**

The clinical parameters of the patients at entry into the two arms were similar (Table 1). Patients tolerated the enema therapy without problems. As expected with limited left-sided disease, full blood count and albumin were usually in the normal range at entry and remained unchanged throughout.

*End-points*

Symptom scores are shown in Figure 1. The symptom score improved in seven of the eight patients in the colostrum group after 4 weeks of treatment (Figure 1; mean response, –2.9; 95% CI, –5.4 to –0.3). In contrast, no significant change in the symptom score of the placebo group was seen (mean response, 0.5; 95% CI, –2.4 to +3.4).

The sigmoidoscopic appearance and histological scoring both showed some improvement in each group (Table 2). However, only the change in the histological score of colostrum-treated patients achieved statistical significance (mean response, –0.9; 95% CI, –1.69 to –0.03), with the equivalent change in the placebo-treated group giving a mean response of 0.2 (95% CI, –2.4 to +2.6).

*Final review*

No early post-therapy rebound of disease was seen in the colostrum-treated patients, as a final review 6 months after the study showed that only one of the eight colostrum-treated patients had relapsed requiring

Table 1. Clinical parameters of patients with colitis restricted to the left side of the colon at entry into the study

	Placebo	Colostrum
<i>n</i>	6 (3 male)	8 (3 male)
Age (years, median, range)	44 (16–75)	46 (20–70)
Time since initial diagnosis of colitis (years)	7 (0.25–29)	7 (0.7–14)
Number already taking 5-ASA prior to start of therapy	4/6	4/8

5-ASA, 5-aminosalicylic acid.

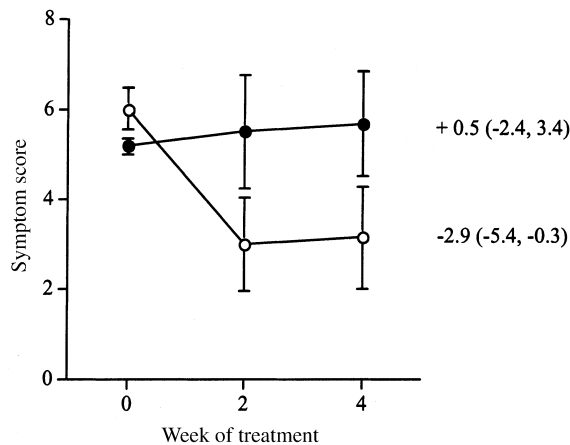


Figure 1. Patients ( $n = 8$ , colostrum, ○;  $n = 6$ , placebo, ●) suffering from colitis restricted to the left side of the colon were randomized to receive twice daily enemas of a defatted colostrum preparation or control solution for 4 weeks. The disease activity<sup>7</sup> is based on a cumulative score of 'patient well-being' as described in the text. Data are presented as the group mean  $\pm$  S.E.M. The mean change and 95% confidence interval for the change at 4 weeks are shown, illustrating that only colostrum caused a significant reduction in score.

steroid therapy, whereas, in placebo-treated subjects, three of the six required steroid therapy over the same period.

## DISCUSSION

We have shown, in this initial study, using a double-blind, randomized protocol, that colostrum enemas induced a rapid reduction in symptom scores and disease remission in a large proportion of patients with active left-sided colitis, when administered in combination with the 5-aminosalicylic acid mesalazine. In contrast, patients receiving mesalazine with placebo enema showed minimal improvement.

Patients were selected on the basis of an acute attack of active colitis that was of sufficient severity to require an

alteration in therapy but not to require admission to hospital. Only patients with disease restricted to the left side of the colon, which accounts for the majority of patients with ulcerative colitis, were recruited to ensure that enema therapy was able to reach the whole of the affected area.

We used the well-validated St Marks system to determine clinical activity,<sup>7</sup> providing an overall score of patient well-being. The resulting score is similar to that of the ulcerative colitis disease activity index,<sup>10</sup> used by other groups, as it analyses similar patient parameters. All patients were required to have a score of five or more to enter the study. Patients who required intravenous steroids or hospitalization were excluded from entry into the study, and patient recruitment was therefore limited to those with mild to moderate disease activity.

Both the local ethics committee and ourselves considered it unethical to leave the patients in the control group without any therapy, and therefore all subjects were given a dose of 1.6 g of mesalazine or, if already taking mesalazine, a dose increment of this amount. 5-Aminosalicylic acid preparations are known to be moderately effective for the treatment of left-sided colitis, giving about a 30–40% response after 4 weeks of therapy.<sup>1</sup> In the present study, patients receiving placebo (plus mesalazine) showed no significant beneficial effect in any of the disease parameters. This lack of major response to mesalazine therapy is likely to be due to the relatively modest additional dose of mesalazine given (1.6 g/day) in order to allow patients already taking the drug to be given the same dose increment as those not receiving any mesalazine at recruitment. Eight of the 14 subjects who entered into the trial were already taking mesalazine at recruitment, with a slightly higher percentage of subjects in the placebo arm (4/6, 66% vs. 4/8, 50%). If the efficacy of mesalazine in inducing improvement/remission is less when given to individuals already taking it, compared

Parameter	Treatment	Pre-treatment	2 weeks	4 weeks
Sigmoidoscopy	Colostrum	2 (2–2)	1 (2–1)	1 (2–0.5)
	Placebo	2 (2–2)	2 (2–1)	1 (2–0)
Histology	Colostrum	2.5 (2–3)	2.5 (1–3)	1 (1–2.75)*
	Placebo	2 (1–3)	1 (1–2.25)	2 (0.75–2.25)

Data are presented as the median (interquartile range). Confidence intervals for changes are given in the text.

\*Indicates  $P < 0.05$  vs. initial values using paired analyses.

Table 2. Effect of colostrum preparation ( $n = 8$ ) or placebo ( $n = 6$ ) enema on sigmoidoscopy and histology scores of patients with colitis restricted to the left side of the colon

to those who are mesalazine naive, this could potentially have confounded our results. We consider this unlikely, however, as sub-group analysis of the four subjects already taking mesalazine in the colostrum treatment arm showed a similar fall in symptom scores (initial median value of 5.5, falling to 2.0 after 4 weeks) to those receiving colostrum who were mesalazine naive. However, numbers were too small to perform formal statistical analyses.

In contrast to the findings in patients given 5-aminosalicylic acid with placebo enema, where no significant improvement in symptom score was seen, patients receiving the colostrum preparation showed a rapid improvement. It is likely that the colostrum acted via several mechanisms, including the stimulation of cell migration (restitution) and proliferation to re-establish epithelial continuity, as we have previously shown these effects when the same preparation of colostrum was used for *in vitro* models of repair.<sup>5</sup> Once achieved, the re-formation of the epithelial barrier is also likely to facilitate subsequent repair by reducing the secondary inflammatory response to luminal antigens. It is also possible that the colostrum preparation stabilized the mucosa to further noxious damage, acting in a cytoprotective manner, as has been shown for epidermal growth factor in preventing gastric damage,<sup>11</sup> although the mechanisms underlying this action are unclear. Follow-up of the patients at the end of the study showed no evidence for a rapid relapse once therapy was stopped, and continued follow-up for about 6 months showed that the vast majority remained in remission.

Growth factors, whether produced by purification or using recombinant technology, are increasingly being used for a variety of clinical conditions. Examples include the use of recombinant human insulin for the treatment of diabetes, erythropoietin for renal failure-induced anaemia and interferon for viral hepatitis. The use of such factors for 'hollow organ' gastrointestinal conditions is at a more preliminary stage. The colostrum preparation used in the current study contains multiple factors that may be important in stimulating the repair process, including epidermal growth factor, transforming growth factors- $\alpha$  and - $\beta$  and interleukin-1 $\beta$ . Studies examining the effect of the administration of individual recombinant peptides, such as epidermal growth factor, platelet-derived growth factor, transforming growth factor- $\beta$  or insulin-like growth factor-I, in animal models of colitis have given encouraging results,

although a beneficial effect is often only seen if administered immediately before the damaging agent.<sup>12</sup> As our study deals with patients who had disease activity at the initiation of therapy, our findings clearly have much greater clinical relevance.

The use of 'natural' products, such as this colostrum preparation, has several potential advantages. We have previously shown that they possess greater intrinsic stability against luminal digestion than isolated individual peptides,<sup>13</sup> and that combination therapy with peptides provides the potential for the stimulation of healing in a synergistic fashion, as shown for lactoferrin and epidermal growth factor in stimulating the growth of the rat intestinal epithelial cell line IEC-18.<sup>14</sup> In support of this idea, our previous *in vitro* studies have suggested that more than one factor in the colostrum preparation is likely to be important in the pro-healing effect, as we found pro-mitogenic and motogenic (restitution) activity in several fractions separated by size-exclusion columns.<sup>5</sup> Furthermore, there is currently a demand from the general public for more 'natural' types of products, which are usually considered as 'alternative therapy', but which can possess potent biological activity. Products such as these are often termed nutraceuticals (from nutrition and pharmaceuticals).

In summary, our finding that a colostrum preparation is able to stimulate remission/repair in a true clinical setting expands on previous *in vitro* and animal model studies and has direct therapeutic relevance. Further studies, including the direct comparison of such preparations with high-dose 5-aminosalicylic acid therapy and steroid therapy and their use in trials of patients in whom steroids need to be avoided, such as in children with inflammatory bowel disease, appear to be warranted.

#### ACKNOWLEDGEMENTS

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