REVIEW

Review of the use of intralesional steroid injections in the management of ileocolonic Crohn's strictures

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ABSTRACT

Most patients with Crohn's disease present with either terminal ileal or colonic disease, with 70% requiring surgery by 10 years after diagnosis. Recurrent stricturing at the anastomotic site is common, often symptomatic and can require re-operation with its inherent risks. Balloon dilation has been shown to provide good symptom relief from such strictures. However, repeat dilations may be required, and further surgical intervention to an anastomotic stricture is needed in up to 30% of cases. Injection of corticosteroids has been suggested as an adjunct to dilation in order to improve outcomes. This paper reviews the current literature on the use of intralesional steroid injections following endoscopic balloon dilation of anastomotic and de novo Crohn's strictures. There have been only two randomised placebo controlled trials and five small non-controlled or retrospective studies. Study numbers vary from 10 to 29 patients. The two randomised trials conflict in their conclusions and numbers are small in these studies. Currently therefore, no firm support can be given to the routine use of intralesional steroid injections.

BACKGROUND

Most patients with Crohn's disease will require surgical resection at some point during their disease process, with reports of over 70% having surgery by 10 years after diagnosis.¹ This most commonly takes the form of ileocolonic resection for distal small bowel disease.² Development of stricturing at the anastomotic site is common, often within the first year after surgery,^{3,4} and can be symptomatic. In the past, this often led to further surgical intervention, with up to 30% requiring a second operation.² De novo strictures can

also develop. Fibrotic strictures form as a result of transmural inflammation, with inflammatory mediators affecting the mesenchymal cells in the mucosa, submucosa and muscle layers of the gut.⁵ Without medical treatment, it has been shown that at 1 year post-ileal resection there are signs of disease recurrence in 73%, increasing to 85% at 3 years.⁶ There is some evidence that medical treatment postoperatively may reduce recurrence, although the evidence is weak, and current UK guidelines suggest that treatment should be aimed at active disease.⁷

Since the 1970s balloon dilation of such strictures has been available, although many need repeat dilations, and may still need to go on to have further surgical interventions.⁸ Injections of steroid agents (betamethasone⁹ or triamcinolone)^{10–15} or antitumour necrosis factor α agents (infliximab)^{16,17} have been used to attempt to reduce the inflammatory processes that led to the development of strictures. As it is suggested that strictures are formed of a combination of chronic fibrotic and inflammatory elements, use of anti-inflammatory agents may reduce the inflammatory element of the stricture. Triamcinolone has been most frequently used, as it remains locally active for up to 1 month. This paper reviews the literature currently available on intralesional steroid injection of Crohn's strictures, for both anastomotic and de novo strictures. In a broader context, we recognise the need to preserve bowel, and to have an awareness of the endoscopic techniques available to do so. Review of balloon dilation techniques is not within the scope of this study, but several review articles can be found elsewhere.^{8,18–23}

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METHODS

Existing guidelines for the management of Crohn's disease were reviewed for recommendations on stricture management.^{7 24–26} A literature search on use of intralesional steroids in Crohn's strictures was performed using PubMed, with search terms Crohn's disease, stricture, endoscopic therapy, and steroid injection. The reference lists of the selected articles were scrutinised for additional papers. A literature review of endoscopic dilation of strictures was also performed (search headings Crohn's disease, strictures, balloon dilation), with papers reviewed for mention of the use of steroid injections during those procedures. A Cochrane library search was performed and no systematic review or meta-analysis exists for this subject.

This review summarises the current literature in the following order: current international guidelines by specialty groups; randomised trials; other studies and case reports in publication date order. Evidence levels are calculated for each study, using the 2011 Oxford Centre for Evidence Based Medicine levels.²⁷

Current recommendations from existing Crohn's disease management guidelines

The current published guidelines^{15–18} for the management of strictures in Crohn's disease are summarised in table 1.

TRIALS: EVIDENCE LEVEL 2

Two small randomised placebo controlled trials with similar study designs have been performed. The first,¹² in 2007 was conducted across two sites over a 4-year period. Thirteen adult patients with short (≤ 5 cm), endoscopically accessible colonic strictures at the ileocolonic anastomosis after right hemicolectomy, who had failed medical therapy with steroids and 5-aminosalicylic acid preparations (5ASA), were randomly selected. The second¹¹ in 2010 was a single site study, randomly assigning 29 paediatric patients over a similar time period, with short (≤ 5 cm) colonic or small bowel strictures (12 at anastomoses, 17 de novo) who had failed medical treatment with 5ASA, azathioprine and cyclosporin. Both studies^{11 12} first

performed balloon dilation of the stricture. East *et al*¹² dilated with a through-the-scope balloon with the aim of dilating to 20 mm, although the decision on the final diameter of dilation was made by the endoscopist. The balloon was held dilated for one period of 1–2 min. Di Nardo *et al*¹¹ also used a through-the-scope balloon and allowed the final diameter of dilation to be decided by the endoscopist, aiming for 18 mm diameter, holding dilation for 3 min. Both studies injected either triamcinolone 40 mg in 5 ml saline, or an identical volume of saline quadrantly into the strictured area. East *et al*¹² repeated injections at 1–2 cm intervals, Di Nardo *et al*¹¹ at 2 cm intervals. Both studies used a second endoscopist to perform the injections in order to protect blinding as the steroid preparation is milky and leakage into the lumen would unblind the colonoscopist.

The results of these trials are summarised in table 2 and they present conflicting results. Di Nardo *et al*,¹¹ in the paediatric population, reported good outcomes in those receiving steroid injection. East *et al*¹² and the adult study, stopped the trial after interim data analysis suggested a trend towards harm with steroid injections. East *et al*¹² found no significant differences between the intervention and placebo groups. One of six in the placebo group and five of seven in the intervention group required redilation.

Di Nardo *et al*¹¹ also described similar intervention and placebo groups, with equal numbers of anastomotic and de novo strictures. One of the intervention group required redilation at an anastomotic stricture. In the placebo group, five went on to redilation or surgery (one anastomotic stricture, four de novo strictures).

These studies are both small, and the differing populations and difference in the stricture origin (all anastomotic in the study by East *et al*,¹² and 12 anastomotic and 17 de novo in the study by Di Nardo *et al*)¹¹ may explain the difference in outcomes. Follow-up was short in both studies. The editorial²⁸ on the paper by East *et al*¹² discussed how it was probably ethically correct to stop the trial early after a tendency (but not a statistically significant figure)

Table 1 Current stricture management guidelines

Guideline	Year	Recommendation
British Society of Paediatric Gastroenterology Hepatology and Nutrition ²⁶	2008	No recommendations about endoscopic management of strictures
American College of Gastroenterology ⁷	2009	Endoscopic dilation can be useful particularly at surgical anastomoses The role of adjunctive corticosteroid injection at the same time is not effective
European Crohn's and Colitis Organisation ²⁴	2010	Endoscopic dilation is a preferred technique for the management of accessible, short (≤ 4 cm) strictures No recommendation or comments about intralesional steroids
British Society of Gastroenterology ²⁵	2010	Endoscopic dilation is an effective and safe treatment for short anastomotic strictures Injection of steroids into the strictures may cause more harm

Table 2 Intralesional steroid randomised controlled trials

Title	Year	Authors	Country	No of patients	Intervention group (n)	Follow-up length (months)	Outcome measures	Successful outcome*	Redilations required	Successful outcome in control group	Intervention group complications
A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures ¹²	2007	East <i>et al</i> ¹²	UK	13	7	12	Time to redilation Time to surgery	2/7	5/7	5/6	2 mild post-dilation bleeds, self-limiting during procedure
Intralesional steroid injection after endoscopic balloon dilation in paediatric Crohn's disease with stricture: a prospective, randomised, double-blind, controlled trial ¹¹	2010	Di Nardo <i>et al</i> ¹¹	Italy	29	15	12	Time free of repeat dilation Time free of surgery	14/15	1/15	9/14	None

*Outcome as defined within the study.

towards harm was demonstrated. Trial cessation does hinder future extrapolation of the data for use in clinical practice and reduces the chances of further funded randomised trials. That study¹² remains the key referenced article behind current American College of Gastroenterology and British Society of Gastroenterology guidance advising against the routine use of intralesional steroid injections.

NON-CONTROLLED TRIALS, RETROSPECTIVE STUDIES AND CASE REPORTS

These are summarised in table 3.

Two papers report case series of stricture management in which steroid injections were used in all the cases reported. In 1995, Ramboer *et al*⁹ reported a series of 13 patients with Crohn's strictures, 12 of which were anastomotic, treated with dilation followed by injection of betamethasone. Most required further dilations, although none needed surgery. However, there were variations in the methods of dilation, length of follow-up, and no indication of the length of stricture, or time to re-dilation (evidence level 4). In 1997, Lavy¹⁴ reported a series of 10 patients who had recurrence of strictures after previous balloon dilation. They were treated with pre-cut needle dilation and injection of triamcinolone, and at 12 months follow-up all were well. Two patients went on to require further dilation and injection after 1 year, with the other eight remaining well (follow up 18–36 months) (evidence level 4).

Several retrospective studies of stricture dilation exist. Many do not comment at all on steroid injections,^{29–30} some report occasional use but do not present any data about their effect.³¹ One paper specifically reports never using intralesional steroids in their unit,³² citing the results of the trial by East *et al*¹² and a lack of larger study evidence as their reasons for this decision. In others, steroid injections may have been used, but this is not uniform across all the cases reported, and is not blinded or placebo controlled. Importantly, they are neither blinded nor placebo controlled trials. These are discussed in more detail below from the earliest publication date forwards.

In 2003, Brooker *et al*¹⁰ reviewed practice in two sites with 14 adult patients undergoing dilation and injection of triamcinolone at anastomotic strictures. Clinical success was an improvement of obstructive symptoms, and avoidance of repeat intervention. Twenty-six dilations were required in 14 patients, and in 20 procedures, steroid injections of between 10 and 40 mg triamcinolone were performed. Seven patients required no further intervention after a single dilation and steroid injection, four patients required multiple dilation procedures due to recurrent obstructive symptoms. The strictures were shorter in the group requiring repeat procedures (maximum 3.5 cm vs maximum 7 cm). Endoscopic

Table 3 Intralesional steroid cases series and reports

Year	1995	1997	2003	2005	2008
Authors	Ramboer <i>et al</i> ⁹	Lavy ¹⁴	Brooker <i>et al</i> ¹⁰	Singh <i>et al</i> ¹⁵	Foster <i>et al</i> ¹³
Country	Belgium	Israel	UK	USA	USA
No of patients	13	10	14	17 (10 received steroid injection)	24 (17 received steroid injection)
Follow-up	Mean 47 months (range 9–73)	Range 18– 36 months	Single intervention—median 16 months (range 13–22) Multiple interventions—median 28 months (range 14–33)	Mean 19 months (range 5–50)	Mean 32 months, median 29 months
Dilation method	Balloon dilation or finger dilation	Pre-cut needle cutting	Balloon dilation	Balloon dilation	Balloon dilation
Steroid injected	Betamethasone	Triamcinolone	Triamcinolone	Triamcinolone	Triamcinolone
Successful outcome	3 (23%)	8 (80%)	7 (50%)	9 (90%)	22 (92%)
Definition of success	Relief of symptoms not requiring further endoscopic or surgical intervention	No further dilations required	Improvement in obstructive symptoms and avoidance of repeat intervention	Improvement in obstructive symptoms and avoidance of repeat dilation or surgical intervention	Substantial enlargement of the lumen and improvement in symptoms
Redilations required	11 (85%)	2 in 2 patients (20%)	4 patients required >1 dilation (29%)	1 (10%)	13 (54%)
Required surgery	None	None	3 (21%)	None	2 (8%)
Complications	None	None	None	1 perforation	None

management failed in three who all required surgery. They concluded that local injection of steroids is safe and may be beneficial with improved outcomes in terms of not needing further procedures. They did acknowledge that azathioprine was started in three out of seven patients in the group with a good response, as opposed to none out of four in the group who required repeat intervention (evidence level 4).

Singh *et al*¹⁵ in 2005 retrospectively reviewed 29 dilations of 20 strictures (13 de novo, seven anastomotic) in 17 patients, with 11 strictures receiving steroid injection. The steroid was injected into the 'most inflamed and narrowed areas of the stricture' suggesting that these cases were selected by severity of the disease. All injected strictures had biopsies confirming active inflammation. They report an immediate success rate of 28/29 (96.5%). Of 17 patients, 13 did not need further dilation or surgery over a mean follow up of 18 months. Of 10 patients receiving steroid injections who did not have a complication (one perforation in the steroid group was reported), there was a 10% recurrence rate. In the group not injected, there were two perforations. In the remaining 16 patients, there was a 31% recurrence rate (evidence level 4).

In 2008 Foster *et al*¹³ reviewed practice in both adult and paediatric cases of small and large bowel strictures in a single centre. Twenty-four patients (22 adults and two paediatric) required 71 dilations to 29 strictures (one stomal, 12 anastomotic, and 16 de novo). Forty-six dilations on 17 strictures were augmented with injection of triamcinolone, with median follow-up 29 months, and median time between dilations 5 months. More than two dilations were required in six out of 29 strictures. Of 24 patients, 22 had initial significant improvement in symptoms without complications, with two reported perforations. Their results do not distinguish outcomes between those receiving steroid injections and those not (evidence level 4).

Practice at the Cleveland Clinic was reviewed in 2007.³³ They report routinely using steroid injections in colonic strictures; this seems to be the case when it is felt that there is active inflammation present (evidence level 5).

A summary of the techniques used for intralesional steroid injection can be found in box 1.

DISCUSSION

In summary, although there are several retrospective reviews, only two small randomised placebo controlled trials have been performed, which come to conflicting conclusions. Numbers are small throughout the literature, tending to be in single centres, or a small number of linked centres. There are variations in techniques used at colonoscopy. There is also

Box 1 Intralesional steroid injection technique

- ▶ Short strictures, successfully dilated
- ▶ 40 mg triamcinolone (40 mg/ml), diluted to 2–5 ml with saline
- ▶ Injected using a standard through-the-scope injection/sclerotherapy needle
- ▶ Inject at distal margin of stricture, or at most inflamed area at endoscopist discretion
- ▶ Quadrantic injections of 0.5–1.0 ml aliquots
- ▶ Repeated at 2 cm intervals along stricture length

much variation between the patient groups, with differences in age, sex, duration of illness and time from surgery. Some papers only include anastomotic strictures; others also include de novo stricturing disease. There is also variation in the concurrent medication used in these patients, from the use of steroids and 5ASA only, to concurrent or failed use of biological agents. Some^{9 10 12 15} but not all studies consider a measure of disease activity, either through the Crohn's disease activity index, blood markers (eg, C-reactive protein and erythrocyte sedimentation rate), macroscopic appearance, or biopsies from the stenotic area. When it is recorded, there seems to be a tendency towards better outcome from steroid injection in those with active disease.^{10 15}

The evidence that intralesional steroid injection reduces recurrence following the endoscopic dilation of Crohn's disease strictures is limited and contradictory. There is currently insufficient evidence^{8 20–23 34 35} to support routine use in clinical practice without a large-scale controlled trial. Such a trial should consider variables such as disease activity, de novo versus anastomotic strictures and dose and type of steroid injection. Given the potential benefit of improved quality of life, reduced need for surgery and reduced cost if an effective strategy can be found, we feel such a trial may be worthwhile, although it would probably require large numbers to show a benefit, and therefore would take a significant amount of time to demonstrate a positive effect. A registry study of existing practice and the concomitant medical treatment of these patients may be a more pragmatic method of assessing the effect of intralesional steroid injections. Currently therefore, no firm support can be given to the routine use of intralesional steroid injections.

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