



Received: 07 July 2016
Accepted: 05 September 2016
First Published: 13 September 2016

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GASTROENTEROLOGY & HEPATOLOGY | RESEARCH ARTICLE

Prognostic factors, effectiveness and safety of endoscopic balloon dilatation for *de novo* and anastomotic strictures in Crohn's disease—A multicenter “real life” study

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Abstract: *Introduction:* Crohn's disease (CD) is a chronic inflammatory disease which is frequently complicated by obstructive symptoms secondary to development of intestinal strictures. The aim of this “real life” study was to assess the effectiveness, safety and outcome of endoscopic balloon dilatation (EBD) in *de novo* vs. anastomotic stenoses. *Patients and methods:* Data of 93 EBDs in 46 CD patients were retrospectively analyzed. Technical success rate was defined as the ability of endoscope to traverse the stenosis after dilatation. Long-term clinical success rate was claimed if a patient remained asymptomatic and did not require surgery or further endoscopic dilatation following the technical success. *Results:* About 62.4% of strictures were *de novo* and 37.6% anastomotic. The elapsed time between diagnosis and the first balloon dilatation was 9.5 (0–35) years. About 73.1% of dilatations were successful over a short-term period without serious complications. About 47.8% of patients showed that EBD is effective over a long-term period. EBD of anastomotic

ABOUT THE AUTHORS

Anita Bálint is a young medical doctor-member of Colorectal Workgroup, 1st Department of Medicine, University of Szeged, Szeged, Hungary—who defended her PhD degree on topic of Inflammatory Bowel Diseases (IBD). Bálint's research activities involves clinical and pharmacotherapeutic studies. She is a regular member of both the Hungarian Gastroenterological Society and the European Crohn's Colitis Organisation (ECCO). Colorectal Workgroup (leader: Tamás Molnár MD, PhD) is one of the most productive research group not just at the 1st Department of Medicine, University of Szeged, than in the country. Research topics include: (1) diagnostic and therapeutic opportunities of IBD, (2) assessment of palliative treatment of gut malignant tumours, (3) investigation of diagnostic utility and effectiveness of gastrointestinal endoscopic interventions. We collaborate with number of researchers outside of 1st Department of Medicine, this cooperation was the basis of several multicenter National and International studies, as well.

PUBLIC INTEREST STATEMENT

Crohn's disease (CD) is a chronic inflammatory bowel disease which is frequently complicated by obstructive symptoms secondary to development of intestinal strictures. Stricture that appears during natural course of CD is defined as *de novo* stricture. Anastomotic stricture occurs after surgical intervention. Treatment of these strictures in gut is surgical or endoscopic intervention. Our aim was to assess effectiveness and safety of endoscopic balloon dilatation (EBD) for *de novo* and anastomotic strictures in CD and to determine factors that affect on effectiveness and outcome of this endoscopic intervention. In this article EBD is an effective therapy of short strictures in CD with low complication rate. Using this endoscopic method we can avoid surgical interventions in most of the cases. According to our results, EBD of anastomotic stenosis may be more preferable than the *de novo* strictures.

strictures showed better outcome than that of *de novo* strictures, however biological therapy before or after dilatation, immunomodulatory therapy and the time between the diagnosis and the first dilatation had no influence on long-term effectiveness. Nine subjects required surgery due to strictures after balloon dilatation. **Conclusion:** The results of this study highlight that EBD is an effective therapy of short strictures in CD with low complication rate. Using this endoscopic method we can avoid surgical interventions in most of the cases. EBD of anastomotic stenosis may be more preferable than that of the *de novo* strictures.

Subjects: Chronic Diseases; Complementary & Alternative Medicine; Gastroenterology

Keywords: Crohn's disease; balloon dilatation; stricture; endoscopy

1. Introduction

One of the major forms of inflammatory bowel diseases is Crohn's disease (CD); this chronic disorder of the intestinal tract with transmural inflammation can occur anywhere from the mouth to the anus, but commonly affects the terminal ileum. The phenotype of CD has been categorized by Montreal classification considering the age at the time of diagnosis, the location and behaviour of the disease (Satsangi, Silverberg, Vermeire, & Colombel, 2006). Main categories of CD behaviour are "non-stricturing, non-penetrating", "stricturing" and "penetrating" depending on the presence or absence of fistulas, abscesses and strictures. It seems that CD behaviour changes over the course of the disease: almost half of CD patients had changed in behaviour over 10 years, mainly from non-stricturing, non-penetrating disease to either stricturing or penetrating disease (Louis et al., 2001). The stricturing form is not common at the diagnosis; however it becomes more frequent over time, which may be the consequence of chronic inflammation with cell death and consecutive scarring (Brenmoehl, Falk, Göke, Schölmerich, & Rogler, 2008). Intestinal strictures may lead to such severe conditions as subileus and ileus, perforation or abscess formation. Despite the advances in the medical therapy of inflammatory bowel diseases, intervention is necessary in the majority of stricturing CD cases as showed by the data in the literature: up to 80% of patients require surgery within 10 years after the diagnosis and the cumulative rate of surgery after 10 years is 64% (Nanda et al., 2013; Wibmer, Kroesen, Gröne, Buhr, & Ritz, 2010). Endoscopic balloon dilatation (EBD) is a minimally invasive therapeutic alternative to surgery in stricturing CD. EBD in stricturing CD is generally performed in the colon and terminal ileum, however advanced techniques like single and double-balloon endoscopy facilitate the access to more oral regions of the small bowel. A technical success rate of 71–100% and a major complication rate of 0–18% have been reported with EBD (Wibmer et al., 2010).

The aim of our 'real life' study was to evaluate the short- and long-term efficacy and the safety of EBD in CD patients with *de novo* and anastomotic strictures.

2. Material and methods

2.1. Patients' characteristics

Ninety-three EBDs were performed to treat 46 CD patients (23 males, 23 females, mean age at first EBD: 38 [18–67] years) in two tertiary centres in Hungary between November 2002 and March 2014. Based on the data from this study population, a retrospective analysis was performed. All patients had an established diagnosis of CD confirmed by clinical, endoscopic and histological criteria; in addition, disease location and behaviour were classified according to the Montreal classification (Silverberg et al., 2005). Inclusion criteria were clinical symptoms of intestinal obstruction, and absence of intestinal fistulas, abscesses, ulcers around the strictures or moderate/severe disease activity. All of our enrolled patients presented symptoms such as prolonged gastric emptying, abdominal pain, cramps, nausea and bloating, furthermore, all of them had *de novo* or anastomotic strictures through which the endoscope could not pass.

Prior to the EBD 22 subjects had undergone surgical bowel resections. About 35 out of 93 dilations were performed due to stricture of intestinal anastomosis.

2.2. Dilatation protocol

All patients had given their written informed consent to the procedure. The endoscopic procedure was chosen on the basis of the location of the stricture. Gastric or duodenal strictures were assessed by gastroscopy. EBD for colonic or ileocolonic strictures was performed by colonoscopy. Conscious sedation was used if the subject requested it. EBD was performed by experienced endoscopists in accordance with protocols. Appropriate laboratory tests were completed before the intervention. Olympus CF-Q165I colonoscopes and Olympus GIF-Q165 or Olympus GIF-2T160 gastroscopes were used for EBD. Dilatations were carried out using through-the-scope balloons (CRE™ Wire-guided oesophageal/colonic Balloon Dilatation Catheter, Boston Scientific, USA) with diameters from 10 to 18 mm. The balloon was led into the stricture under visual control. After having reached the correct position of the balloon, it was insufflated with air (under 2 atmospheric pressure) for 2–3 min; this procedure was repeated for several times until the endoscope could pass through the stenosis – 3 attempts were made on average. Technical/short-term failure was obtained if the balloon did not reach the correct position or if despite the multistep inflation, the diameter of bowel did not change significantly.

To inquire any EBD-related complications, patients were observed in our hospital overnight.

2.3. Definitions

Short-term (technical) success was defined as the ability of the routinely used 12 mm diameter sized endoscope to pass the stenosis after dilatation.

Long-term clinical success (outcome) was claimed if a patient remained asymptomatic and did not require surgery or further endoscopic dilatation, following technical success.

2.4. Statistical analysis

Categorical variables are presented as counts (percentages), continuous variables are presented in mean (range) format. The collected data were analyzed using χ^2 test, Fisher's exact test and logistic regression analysis. For multiple comparisons ANOVA was carried out and followed by Bonferroni *post hoc* tests. Pairwise comparisons were performed on estimated marginal means by considering the presence or absence of interaction. $p < 0.05$ was considered as statistically significant. The surgery-free survival curve was constructed with the nonparametric Kaplan-Meier estimator with accompanying 95% confidence interval. Dividing simply the number of patients undergoing surgery (9) by the total number of patients (46), i.e. calculating simply a frequency is not the sound way to calculate the risk of surgery as we are dealing with data involving the follow-up of patients. The problem with this logic is that it assumes that all patients contribute 1/46, but this is not correct in this setting: after the first patient underwent surgery, the at-risk population consists only of 45 patients, thus the second patient contributes 1/45 and so on. This is just the central logic of Kaplan-Meier survival analysis, where the at-risk population is always reduced whenever an end point (or censoring) happens. Our calculation is consistent with the statistical practice in this field (Wibmer et al., 2010). The statistical analysis was performed using R statistical software (version 3.1.0).

3. Results

3.1. Patients and strictures characteristics

Overall, 93 EBDs were performed on 50 strictures in 46 subjects. Patients and disease characteristics are shown in Table 1. The mean duration of CD was 9.5 years. The mean age of the patients was 25 (8–59) years at the time of diagnosis of CD. Colonic and ileocolonic location and stricturing behaviour

at diagnosis were the most frequent phenotypes of CD (Table 1.). However, some patients changed in disease behaviour over the time; in our cohort there were 11 subjects with non-stricturing, non-penetrating and 8 subjects with penetrating disease behaviour at the diagnosis of CD. A great proportion (84.9%) of dilatation was performed in the lower gastrointestinal tract (79 of 93). The mean time between the diagnosis and the development of strictures with symptoms was 7.3 (0–27) years. The time between the diagnosis of CD and the first balloon dilatation was 9.5 (0–35) years, therefore the elapsed time between stenotizing symptoms and EBD was 2.98 (0–17) years. The mean time between bowel resection and the first EBD was 82 (14–228) months in patients with anastomotic strictures (Figure 1). Fifty-eight (62.4%) EBDs were performed on *de novo* strictures and 35 (37.6%) on anastomotic ones. None of the strictures length was beyond used balloon length (5.5 cm). In *de novo* group the elapsed time between first stricturing symptoms and EBD was 2 (0–9) years, while in the anastomotic group it was 4 (0–17) years. Forty patients were on medical therapy at the time of

Figure 1. Patients and strictures characteristics.

Notes: The mean time between the diagnosis and the development of strictures with symptoms was 7.04 and 7.6 years in *de novo* and anastomotic strictures, respectively. The elapsed time between the diagnosis and the first balloon dilatation was 8.7 and 10.4 years, respectively. The mean time between diagnosis and colon resection was 4 years in patients with anastomotic strictures. The mean time between bowel resection and the first EBD was 6.83 years in patients with anastomotic strictures.

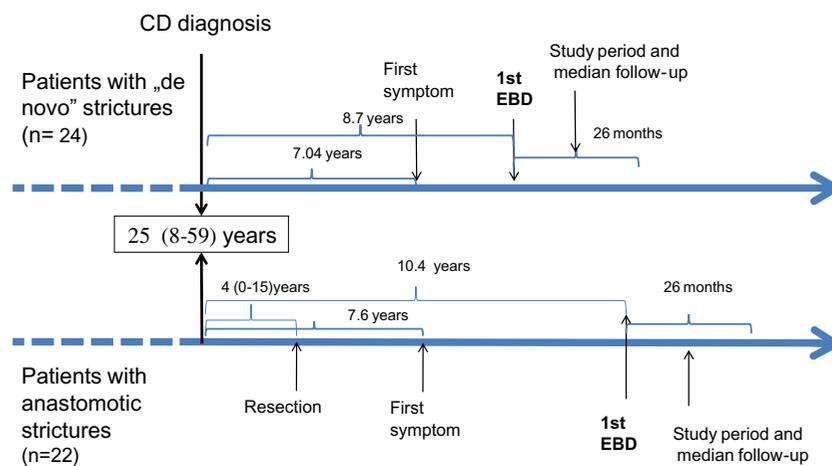


Figure 2. Likelihood of surgery free survival among our patients.

Notes: Overall, 9 out of 46 dilated subjects underwent surgery during the follow-up period. The mean surgery free survival time was 78 months (95% CI: 59–98 months). The Kaplan–Meier curve shows that at month 12 approximately 90% of patients, at month 24 approximately 80% of patients was surgery free; however after 50 months the surgery free rate was 60.7%.

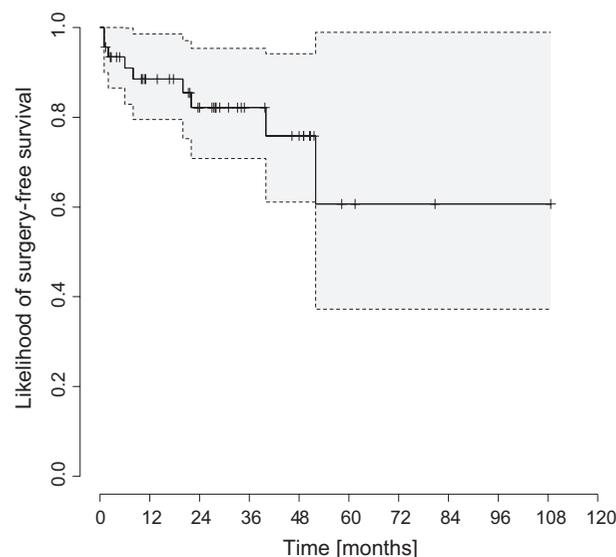


Table 1. Clinical data of enrolled patients

	No.
Enrolled patients	46
Gender (male/female)	23/23
Disease localisation at diagnosis	
L1	7
L2	16
L3	15
L4	2
L1 + L4	3
L2 + L4	3
Disease behaviour at diagnosis	
B1	11
B2	20
B3	8
B2 + B3	3
Data missing	4
Smoking status	
No	19
Yes	5
Stopped	11
Data missing	11
Disease duration at first EBD (years)	9.5 (0–35)
Age at first EBD (mean [min–max] years)	34.2 (13–67)
Time between diagnosis and development of stricture symptoms (mean [min–max] years)	7.3 (0–27)
Medical therapy at the time of first EBD	
No treatment	5
5-ASA	22
Azathioprine	16
Corticosteroids	12
Anti-TNF- α	8
Metothrexate	2
Topical steroid	2
Antibiotics	10
Proton-pump inhibitors	11
No. of strictures	50
No. of dilatations	93
<i>De novo</i>	58
Anastomotic	35
Surgery after EBD	9

the first EBD: 22 patients received 5-aminosalicylic, 16 azathioprine and 12 corticosteroid therapy. Eight patients were on anti-TNF therapy at the time of the first EBD; although 21 patients received anti-TNF agent before the first EBD. After the first EBD, anti-TNF therapy was started in 24 cases. Only five patients were smokers.

3.2. Short-term outcome/technical success

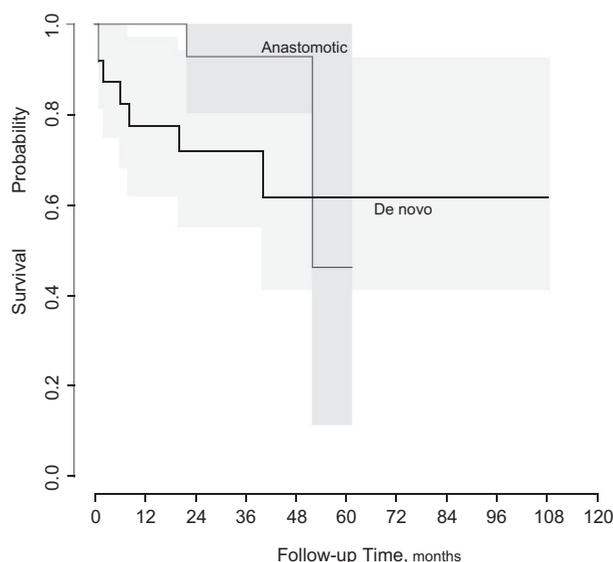
Technical success was achieved in 73.1% of the dilatations. According to the number of cases, technical success rate of the first EBD was 73.9%. In Fisher's exact test, the type of stricture (*de novo* vs. anastomotic) did not have an influence on the short-term efficacy of EBD ($p = 0.999$). Dilatations were performed without serious complications.

3.3. Long-term outcome

The median follow-up of the patients was 26 (1–109) months. Twenty-two subjects sustained response to a single dilatation, with avoidance of further EBD or surgical interventions during the follow-up time. Thus, EBD showed long-term success in 47.8% of our patients. However, re-strictures occurred in 20 subjects during the observation period. Re-dilatation was performed in all patients with re-strictures: seven patients had two dilatations, 8 patients had three dilatations and 5 patients had more than three dilatations. The average number of EBD was 3.3 in this subgroup of patients. The mean time between the first and the second EBD was 11.1 (0–40) months, it was 10.9 (0–42) months between the second and the third, and 16.6 (5–51) months between the third and the fourth dilatation. The mean time between dilatations was 9.96 (1–16.6) months. The elapsed time between the diagnosis and the first balloon dilatation, the mean time between the diagnosis and the development of strictures with symptoms, gender, age and smoking status had no influence on long-term clinical success ($p = 0.714$, $p = 0.942$, $p = 0.751$, $p = 0.685$, $p = 0.322$). No association was found between disease location and the number of EBD/subject ($p = 0.39$), behaviour and number of EBD/subject ($p = 0.21$). Anti-TNF therapy before and after EBD did not have an influence on long-term success ($p = 0.99$ and $p = 0.99$, respectively), nor on the number of dilatations ($p = 0.11$). Overall, 19 subjects were on immunomodulatory therapy at the time of the first EBD. In logistic regression, medication (immunosuppressants, anti-TNF, both or none of them) were not associated with long-term success in our study ($p = 0.29$). Depending on the type of the stricture, an interesting difference was found regarding the outcome: long-term success rate was 29.2% in the *de novo* group and 68.2% in the anastomotic group ($p = 0.02$). Less patients needed surgery in the anastomotic group (*de novo* group: 20.8% vs. anastomotic group: 9.1%; $p = 0.07$); however, the number of dilatations did not depend on the stricture type (mean number of dilatations was 2.3 in *de novo* vs. 1.7 in anastomotic group; $p = 0.2$). Overall, 9 out of 46 dilated subjects underwent surgery as the subsequent therapeutic option indicated by strictures. Cumulative recurrence estimates from survival analyses were used to determine surgery free survival. According to our data, the mean surgery free survival time was 78 months (95% CI: 59–98 months). In the first year 90% of patients, and in second year 80% of them managed to avoid surgical procedures, however after 50 months the surgery free rate was only 60.7% (Figure 2). Surgery free survival rate did not differ significantly between *de novo* and

Figure 3. Likelihood of surgery free survival among patients with *de novo* and anastomotic strictures.

Notes: Less patients needed surgery in the anastomotic group. The Kaplan-Meier curve shows that at month 12 approximately 80% of patients with *de novo* and 100% of patients with anastomotic strictures was surgery free.



anastomotic group (0.099 by log rank test); however, statistical comparison of groups is limited, because of small number of subject who underwent surgery (Figure 3).

3.4. Safety

Dilatations were performed without perforations or other significant complications such as gastrointestinal bleeding with need for blood transfusion or abdominal pain requiring hospitalization; however, a minority of subjects developed slight bleeding in the area of the dilatation, which resolved spontaneously.

4. Discussion

The outcomes of medical treatment of stricturing CD are poor due to the reduced ability to control the progress of fibrosis (Samimi, Flasar, Kavic, Tracy, & Cross, 2010), and the risk of recurrence after intestinal resection is high, thus the management of *de novo* and postoperative intestinal strictures is a relevant issue (Greenstein, Sachar, Pasternack, & Janowitz, 1975; Rutgeerts et al., 1990).

In recent years EBD has become a relatively easy and quick to perform procedure for managing intestinal strictures with high success rate. It offers some advantages as being minimally invasive, it saves the intestinal length avoiding short-bowel syndrome, and avoids risks associated with general anaesthesia.

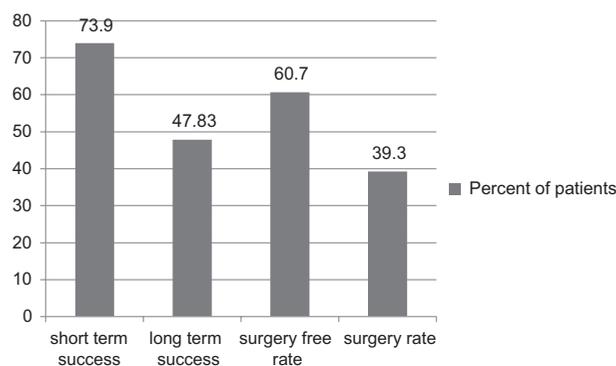
As stated in our research, several other studies also reported that EBD can be a safe alternative to surgical resection or stricturoplasty (Couckuyt, Gevers, Coremans, Hiele, & Rutgeerts, 1995; Ferlitsch et al., 2006; Karstensen, Hendel, & Vilmann, 2012; Mueller, Rieder, Bechtner, & Pfeiffer, 2010). There were no fatal complications in the reported studies. Major complication rates in a review ranged from 0 to 18% with a median of 3% (Karstensen et al., 2012). As a matter of fact, in literature, higher complication rates were observed using larger balloon diameters and more frequent dilatations (Couckuyt et al., 1995; Gustavsson et al., 2012). Balloons with a diameter of 10–18 mm were used depending on the stricture, and they were insufflated by a multistep inflation with air [2 ATM pressure that is slightly smaller than the one in manufacturer's instruction (3.4–10 ATM)] and this stepwise technique seems to be safe and effective. One of the limitations of this procedure is the length of the stricture, as reported that the main field of application is up to 5 cm of length (short strictures) (Hassan et al., 2007; Mueller et al., 2010). Technical success was 73.1% in our cohort; that is in accordance with the results of other studies (71–100%) (Scimeca et al., 2011; Wibmer et al., 2010). However, 44.4% of our patients had more than one dilatation, which showed that EBD could be safely repeated and may obtain a symptomatic relief after further dilatations. Long-term success was 47.8% in our study, therefore almost half of the patients remained asymptomatic after the first dilatation; however, repeated EBDs led most of the remaining patients to be asymptomatic resulting in a surgery-free outcome during the follow-up period. In this study the post EBD surgical rate (39.3%) was slightly higher, compared to others with the mean of 28.5% (Wibmer et al., 2010). The long-term success rate after a single dilatation varies between 21 and 51% in the literature (Honzawa et al., 2013; Nanda et al., 2013; Scimeca et al., 2011). A meta-analysis by Hassan et al. (2007) showed a short-term success rate of overall 86% with complication rates of 0–11%, and the long-term efficacy was 58%. Some studies suggest an association between technical success and long-term outcome: technical success predicts a lower rate of surgery (Scimeca et al., 2011). Hassan's review showed that 89% of those subjects for whom EBD was not successful technically, surgical intervention were needed. In our study, 4 out of 9 patients (44.4%) who underwent a surgical procedure had technically failed EBD. Long-term data on the outcomes and parameters predictive of success are not obvious, and the influencing factors are largely unclear. As mentioned above, technical success and short strictures (Couckuyt et al., 1995; Scimeca et al., 2011) as well as absence of ulcers in the stricture were found to be beneficial prognostic factors of outcome (Endo et al., 2013). Recurrence of postoperative CD stricture is common, as the study population showed: more than one third of patients had anastomotic strictures. As theoretically expected, a significantly favourable long-term outcome was observed in the anastomotic group in our study. Shorter length and less severe mucosal and transmural inflammation may explain the higher success rate. There is no clear evidence

about the therapy after dilatation. Some authors suggest the efficacy of certain agents like the combination of budesonide and azathioprine (Raedler, Peters, & Schreiber, 1997), but others did not prove it (Nanda et al., 2013; Ono et al., 2012; Thienpont et al., 2010; Thomas-Gibson et al., 2003). Views regarding the influence of anti-TNF agents on strictures have been conflicting (Nakazato, Oku, Yamane, Tsuruta, & Suzuki, 2002; Theiss, Simmons, Jobin, & Lund, 2005; Vassallo, Matteson, & Thomas, 2002). We did not confirm any association between EBD and medication of CD; neither the use of anti-TNF before or after EBD, nor immunosuppressants were predictive factors for long-term outcome of EBD. In addition, anti-TNF therapy did not show association with the number of dilatations. Analysis of data from 25 patients by Honzawa et al. (2013) showed significant difference in the mean number of dilation procedures per patient between the early immunomodulatory drug induction and post-immunomodulatory drug-induction groups, although no significant difference in the cumulative non-surgical rate was observed between the two groups. A study from Belgium also confirms that none of the therapies were associated with an increased risk of surgical relapse (Thienpont et al., 2010). An outstanding question is the timing of the procedure, whether the elapsed time between the diagnosis and the first EBD or the one between the development of strictures and the first EBD has an influence on effectiveness. Our results highlight that the above mentioned factors did not predict the successfulness of EBD, thus despite the elapsed time it could be performed with a good chance in every eligible patients.

The main limitation of our study is small number of subject, however sufficient number of dilatations enabled to performe conclusive statistical analysis. Results showed clearly that EBD is an effective tool to avoid surgical interventions in most of the cases, and its use may be more preferable in case of anastomotic stenoses than the *de novo* strictures. Another limitation was that CT or MRI examination wasn't done in every case, thus length of strictures was estimated only by endoscope. We used through-the-scope balloons with diameters from 10 to 18 mm and length of 5.5 cm. None of the strictures was beyond used balloon length (5.5 cm).

In summary, our results showed high technical success rate with a decreased need of surgery during the follow-up period. However, in 20 of 46 cases, multiple dilatations were needed to avoid surgical intervention. On the other hand, these multiple interventions did not impair the good safety profile of EBD resulting in a 60.7% surgery-free rate during the more than 3 years follow-up period (Figure 4). A study from Japan showed that EBD for small bowel strictures secondary to CD provides success for short and long-term efficacy as well; however, the high re-dilatation rate is one of the clinical problems of this procedure (Hirai et al., 2014). We did not find predictive factors for long-term success except the type of stenosis, as the immunosuppressive status of patients, medication, disease duration, and elapsed time between EBD and the development of strictures did not influence the efficacy of EBD. Thus, in the light of these findings, EBD is an effective therapy of short strictures in CD with low complication rate mainly in case of postsurgical anastomotic Ruttgeert's score of 4 points recurrence (Sostegni et al., 2003). Our recommendation is the use of pneumatic balloons

Figure 4. Overall efficacy of EBD: 73.9% of patients showed technical success at the first EBD and 47.8% of patients showed that endoscopic balloon dilatation is effective over a long-term period i.e. at the end of the median 26 (range, 1–109) months follow-up period.



Note: Nevertheless, at the end of follow-up period the surgery free rate was 60.7%.

insufflated by a multistep inflation due to its excellent safety profile. Fibrotic complications remained the vague field of CD, thus there is a need for further research to improve therapy and reduce hospitalization rates; however, by using this endoscopic method we can avoid surgical interventions in most of the cases.

Funding

This work was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences [grant number BO/00632/14/5]; TAMOP [grant number TAMOP-4.2.2.A-11/1/KONV-2012-0035], [grant number TAMOP-4.2.2.A-11/1/KONV-2012-0052], [grant number TAMOP-4.2.2.A-11/1/KONV-2012-0073]. Also Klaudia Farkas was supported by Országos Tudományos Kutatási Alapprogramok [grant number OTKA PD 105948].

Competing Interests

The authors declare no competing interest.

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Citation information

Cite this article as: Prognostic factors, effectiveness and safety of endoscopic balloon dilatation for de novo and anastomotic strictures in Crohn's disease—A multicenter “real life” study, Anita Bálint, Dalma Töröcsik, Károly Palatka, Zoltán Szepes, Mónika Szűcs, Ferenc Tamás, Ferenc Nagy, Klaudia Farkas, Anna Fábán, Renáta Bor, Ágnes Milassin, Mariann Rutka & Tamás Molnár, *Cogent Medicine* (2016), 3: 1233687.

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