Alimentary Tract

Short term colectomy rate and mortality for severe ulcerative colitis in the last 40 years. Has something changed?

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A R T I C L E   I N F O
Article history:
Received 26 September 2015
Accepted 22 December 2015
Available online xxx

Keywords:
Colectomy
Mortality
Severe ulcerative colitis

A B S T R A C T

Background: About 20% of ulcerative colitis patients will experience a severe attack during the course of the disease. Intensive treatment, early surgery and, more recently, “rescue therapies” improved prognosis.
Aims: To evaluate in-hospital colectomy and mortality rates for severe ulcerative colitis over 40 years in two referral centres.
Methods: All in-patients with severe ulcerative colitis from 1976 to 2010 were considered. 159 patients were assigned to 4 cohorts: cohort 1 n=34 (1976–1980); cohort 2 n=29 (1986–1990); cohort 3 n=45 (1996–2000); cohort 4 n=51 (2006–2010).
Results: The colectomy rate was 64.7%, 62.0%, 44.4% and 9.8%, respectively, in the four cohorts (p < 0.0001). The mortality rate decreased from 8.8% in cohort 1, to 0 in cohort 4 (p = 0.04). Infliximab was used only in cohort 4 (17 patients).
Conclusions: A significant reduction of colectomy and mortality rates in severe ulcerative colitis was observed in the last 40 years. Better management of patients, reduced attitude to operate severe ulcerative colitis, as well as the use of Infliximab in the last cohort, all could have contributed to the improved outcome.

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1. Introduction

Approximately 15–20% of ulcerative colitis (UC) patients will experience a severe attack during the course of the disease [1]. Severe UC is a potentially life-threatening condition, that must be promptly recognized and managed in hospital. Early recognition of negative prognostic factors, intensive medical therapy, and early surgery for non-responders all contributed to the improved outcome in the last decades [2] and mortality for UC is at present minimal [2]. In the pre-steroid era mortality was 22% in the first year after diagnosis [3], but decreased to 7% after the introduction of steroids [4]. In the seventies, the introduction of the so called “Oxford regimen”, led to a further decrease of mortality to less than 2%, with a colectomy rate of approximately 30% [5–12]. Mortality is largely dependent upon severe acute complications, such as toxic megacolon (TMC), massive rectal bleeding, multiple organ dysfunction syndrome (MODS) or to surgical complications [13] and is particularly relevant in elderly patients with multiple comorbidities [14]. In non-referral centres, mortality after urgent colectomy is still a problem. Recent population-based nationwide studies carried out in United Kingdom, USA and Denmark, report a 30-day mortality rate after urgent colectomy of approximately 5% [13–16].

In spite of intensive intravenous glucocorticoid treatment, the short term colectomy rate remained stable over the last 30 years [17], as approximately 20–30% of patients fail to respond and require surgery. Moreover, one third of those patients, who escape early colectomy, will eventually require surgery, due to further severe attacks or relapsing disease [18].

Surgery is considered curative in UC, but the quality of life after restorative protocolectomy is generally poorer than that of patients responding to medical therapy [19]. Thus, different rescue strategies were proposed to avoid surgery in non-responders, without affecting the mortality rate. In the nineties intravenous (iv) cyclosporine (CyA) has been proposed as “rescue therapy” for these patients [20]. This led to high short term remission rates, but colectomy was delayed more than prevented. Indeed approximately 50% of patients treated with CyA will eventually require colectomy [21]. Moreover, CyA is burdened by the risk of severe side-effects, including death. More recently, infliximab (IFX), a chimeric
monoclonal antibody anti-tumour necrosis factor-α (TNF-α), has been used as "rescue therapy" in severe steroid-refractory UC. A single 5 mg/kg infusion of IFX reduced the colectomy rate by 40% within 3 months in a Scandinavian randomized placebo-controlled trial [18]. Although the benefits of the "rescue therapy" with IFX remain in the subsequent 3-year follow-up [22], few data are available about long-term benefits. Open label series with different length follow-up and different IFX doses report an overall colectomy rate ranging from 18% to 75% [23–28].

The aim of our study was to evaluate the early colectomy rate and in-hospital mortality for acute severe UC over the last 40 years in two referral centres, and to explore the impact of "rescue therapies" on surgery and mortality rates.

2. Materials and methods

Four phases, from 1976 to 2010, were considered representative of pivotal changes in the management of acute severe colitis, from the introduction of the "Oxford regimen", to the institution of "rescue therapies" with biologics.

The records of all the 159 patients admitted to the hospital for a severe attack of UC in two referral Gastrointestinal Units in Rome (Department of Internal Medicine and Medical Specialties of “Sapienza” University and “San Filippo Neri” Hospital) in four 5-year cohorts were reviewed. Patients were stratified, according to the calendar period of hospital admission: cohort 1 (1976–1980); cohort 2 (1986–1990); cohort 3 (1996–2000); cohort 4 (2006–2010). The diagnosis of UC was established according to standard criteria [29]. A severe attack was defined according to Truelove and Witts, modified by Chapman, as the passage of >6 bloody stools daily with at least one of the following criteria: temperature >37.8°C, pulse rate >90/min, haemoglobin <10.5 g/dl or erythrocyte sedimentation rate (ESR) >30 mm/h [30].

Clinical and demographic characteristics of all patients were recorded upon admission, including age, gender, disease duration, disease extension and bowel movements. Laboratory data included haemoglobin (Hb), erythrocyte sedimentation rate (ESR), white blood cells, serum albumin and arterial pH. The occurrence of local or systemic complications at admission or during the hospital stay was also recorded: toxic megacolon, "impending megacolon", massive rectal bleeding and multiple organ dysfunction syndrome. Gastrointestinal gas distension was evaluated on plain abdominal X-rays. Toxic megacolon was defined as dilatation of the transverse colon exceeding 6 cm in diameter [31] and "impending megacolon" as an increased colonic gas content (<6 cm) and/or persistent gas distention of small bowel loops [32].

All patients in the four cohorts were treated according to a standard regimen: intravenous (iv) steroids (hydrocortisone 100 mg qid or 6-methylprednisolone 60 mg/day), rectal steroids, fluid-electrolytes and albumin replacement, when needed. Total parenteral nutrition and blood transfusions were used if appropriate, and antibiotics were administered according to clinical judgement. Colectomy was performed in patients who failed to respond to iv steroids and in patients who deteriorated or developed complications during the steroid treatment. Infliximab was used as "rescue therapy" for patients who failed to respond to iv steroids only in the cohort 4.

The co-primary end points were early colectomy rate, defined as surgery performed within two months from hospital admission, and in-hospital mortality.

2.1. Statistical analysis

Kruskal–Wallis test was used to compare median values between groups. Chi-square test was used when appropriate. A p value <0.05 was considered statistically significant. Stats Direct statistical tools (Copyright © 1990–2001) was used for all calculations.

3. Results

All the 159 patients admitted to the two Institutions for acute severe UC were enrolled and stratified in four cohorts, according to the calendar period of hospital admission: cohort 1 (1976–1980) n = 34; cohort 2 (1986–1990) n = 29; cohort 3 (1996–2000) n = 45; cohort 4 (2006–2010) n = 51. The clinical and demographic characteristics of patients are shown in Table 1.

The characteristics of patients were slightly different across the 4 cohorts: an older age at admission was observed in cohort 4, compared to other cohorts (p = 0.048) and a lower number of bowel movements in cohort 1 (p = 0.01) (Table 1). Overall, the disease was less severe in more recent cohorts, as suggested by a lower occurrence of local or systemic complications (toxic megacolon, massive rectal bleeding and multiple organ dysfunction syndrome), 38%, 24%, 17.7% and 15.6% in cohorts 1, 2, 3 and 4, respectively (p <0.0001). Toxic megacolon occurred in 32%, 17.2%, 17.7% and 9.8% of patients in cohorts 1, 2, 3 and 4, respectively (p = 0.0063).

In cohort 4, 17 patients received infliximab as "rescue therapy". Infliximab was administered after a mean of 8.8 ± 4.1 days, after iv steroid regimen. All infliximab treated patients achieved clinical response and none required colectomy during hospitalization.

The early colectomy rate was 64.7% (22/34), 62.0% (18/29), 44.4% (20/45) and 9.8% (5/51) in cohort 1, 2, 3 and 4, respectively (p <0.0001) (Fig. 1), showing a significant reduction in early need for surgery in more recent years. However when considering the subgroup of patients with complicated disease at admission or who developed local or systemic complications during the hospital stay (36/159), the early colectomy rate was similar across the 4 cohorts: 84.6% (11/13), 71.4% (5/7), 87.5% (7/8) and 50% (4/8) in cohort 1, 2, 3 and 4 respectively (p = 0.025) (Fig. 2). Conversely, the early colectomy rate is significantly reduced across cohorts in the subgroup of patients with severe, but uncomplicated disease: 47.8% (11/21) in cohort 1 and 2.3% (1/43) in the cohort 4 (p <0.0001) (Fig. 2).
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Fig. 1. Significant reduction over time in the colectomy rate in patients with severe UC ($p < 0.0001$). On the column are reported the overall number of patients in each group.

Fig. 2. Variation over time in the colectomy rate in uncomplicated severe UC compared with complicated patients presenting with toxic megacolon, massive bleeding and MODS. The early colectomy rate is significantly reduced only in the subgroup of patients with severe, but uncomplicated disease ($p < 0.0001$).

Noteworthy, in this subgroup of patients with uncomplicated disease, the most relevant reduction in the early colectomy rate was observed in those with impending megacolon: 88.8% (8/9) in the cohort 1 and 5.5% (1/18) in the cohort 4 ($p < 0.0001$) (Fig. 3), suggesting a more conservative approach in more recent years in patient who, although non responders, showed no acute complications. A significant reduction of in-hospital mortality was observed: the in-hospital perioperative mortality rate was 8.8% (3/34) in cohort 1, 6.8% (2/29) in cohort 2, 4.4% (2/45) in cohort 3 and 0% in cohort 4 ($\chi^2$ for trend $p = 0.04$) (Fig. 4). In cohort 1, one patient died for sepsis, one for shock and the other one for massive rectal bleeding, in the cohort 2 one died for acute hepatitis and one for TMC. In cohort 3 one patient died of MODS and one for TMC.

4. Discussion

The analysis of data from 5-year cohorts of patients with severe UC in two tertiary referral centres, confirms the progressive improvement in the short term prognosis over the last 40 years. The choice to analyze data from four, separate, 5-year cohorts, was decided to maximize differences occurring over time. The first period (1976–1980) was characterized by the strict use of the “5 days Oxford regimen”, for the first time published in 1974 [5], which represents a cornerstone in the management of acute severe colitis. In the second and third period (1986–1990, 1996–2000) the intensive steroid treatment was prolonged up to 10 days, according to the physician’s judgement [33,34]. Intravenous cyclosporine [20] was never used as “rescue therapy” for steroid refractory UC in our Institutions. In the fourth period (2006–2010) infliximab became available in Italy and was used as a “rescue therapy”.

In the present series, the overall early colectomy rate dropped from 64.7% in the first cohort, to 9.8% in the last one. These figures are in keeping with those reported in the literature, ranging from 30% to 70% immediately after the introduction of the “Oxford Regimen” [11,12] to 10–30% in more recent series [27,28,35]. The reduction likely results from the improved efficacy of medical treatment, the early recognition of unfavourable prognostic factors and the use of “rescue therapies”. Indeed, before the introduction of “rescue therapies” colectomy was performed in all severe patients failing to respond to intravenous steroids. In 2005 Janner published the results of a small randomized controlled trial on 45 patients with moderate to severe UC, receiving IFX or placebo after the failure of intravenous steroids. Within 3 months, 29.2% of patients treated with IFX, and 96% with placebo, underwent colectomy ($p = 0.017$) [36]. A meta-analysis and systematic review of randomized clinical trials (RCTs) and observational studies on the efficacy of IFX in reducing hospitalizations and surgery, concluded that, IFX reduced the risk of surgery in RCTs, (OR, 0.57; 95% CI, 0.37–0.88), but not in pooled observational studies. Several factors, including probably more marked severity in real-life studies, likely accounts for the difference. The observation is clinically and economically relevant, as hospitalization and surgery markedly contribute to the total direct costs associated with IBD [37]. In a large retrospective multicenter study on 211 IFX-treated UC patients, hospitalized between 1999 and 2010, the probability of colectomy–free survival at 3 months was 0.71. Forty-eight (64%) operations were carried out during the first 14 days,
suggesting the need for optimizing rescue strategies in patients who fail to respond to steroids [38]. Similarly, between 1997 and 2009, a reduction in elective, but not emergent colectomies was reported, with an average annual change of −7.4% and an inverse trend with the use of immunosuppressants and biologics [39]. Conversely, in the present series of patients hospitalized for severe UC, a significant reduction was observed over time also for urgent/emergent colectomies (from 64.7% in the first cohort to 9.8% in the last one).

Colectomy is considered as a failure of medical therapy in those cases refractory to intravenous steroids or who do not respond to “rescue therapies”, but represents the first line option in patients who develop complications such as TMC, massive rectal bleeding and MODS [40,41]. Thus, the reduced rate of colectomies in the different cohorts herewith reported, could be attributed to different factors.

As previously pointed out, the introduction of “rescue therapy” with IFX is likely central in this result.

Second, patients in the last cohorts had less severe disease, than those in the earlier groups. This is not the case in the present study, as the different cohorts were similar in term of severity, evaluated on the base of clinical and laboratory data, despite higher arterial pH values in the first and third cohort. The number of bowel movements may instead be misleading as the non-significantly lower number in cohort 1 likely reflects the condition of dynamic ileus in patients with toxic megacolon.

Third, a reduced rate of “complicated” UC would also lead to the same effect. Indeed in our series, a progressive reduction in the incidence of complications was observed over time (from 38% in the first cohort to 15.6% in the last cohort). More so the incidence of patients presenting with toxic megacolon (32% in the first cohort and 9.8% in the last cohort). The difference was statistically significant and likely contributed in reducing the need for surgery in the last cohorts.

Finally, one more possible explanation for the reduced colectomy rate over time resides in the more aggressive approach in “high-risk patients”, in the earlier cohorts. So-called “impending megacolon”, consisting in the occurrence of gas distension of the small bowel loop, resulting from a paralytic ileum, often precedes full-blown colonic dilatation [32]. This finding characterizes patients with poorer response to medical therapy and high risk for local or systemic complications, TMC included. In a previous study [42], an aggressive therapeutic approach was advocated. About half of patients with impending megacolon, underwent colectomy, with significant reduction of the mortality rate in comparison to earlier series [42]. In the present study, the colectomy rate showed a progressive decrease from early to late cohorts, in all patients with uncomplicated disease (from 52.3% in the first cohort to 2.3% in the last cohort, p < 0.0001). More so in the subgroup of those presenting with “impending megacolon” (from 88.8% in the first cohort to 5.5% in the last cohort, p < 0.0001).

The in-hospital mortality dropped from 8.8% in the first cohort, to 0 in the last one.

Before the introduction of the “Oxford Intensive Regimen”, approximately 30% of patients with UC, died in the first year after diagnosis [4]. The introduction of the “Oxford Intensive Regimen”, reduced mortality rate to 7% [5]. In the last twenty years, the overall mortality rate of UC patients further declined and does not differ from that of the general population [43], with a pooled standardized mortality ratio of 1.1 [44]. Conversely, recent data from English and American studies reported a 30-days mortality rate of 5.2–5.7% after emergent colectomy and 0.7–0.9% after elective colectomy [13–15,44–46]. Indeed, an increased risk of death is reported in old patients with comorbidities, undergoing emergency surgery 8 days or more from hospitalization, and in hospitals with low colectomy volume [16]. In our study the mortality rate was similar to that reported in studies from the same period, in cohorts 1 and 2 (8.8% and 6.8%, respectively). In cohorts 3 and 4 mortality was lower than that of comparable series (4.4% and 0%, respectively).

In conclusions, despite limitations deriving from the retrospective collection of data, the present study reports a significant reduction in short term colectomies and in-hospital mortality over 40 years in 4 large cohorts of patients, hospitalized for severe UC. Several differing factors likely contributed to the progressively improving outcome, and the reduction of fatal outcomes and need for surgery, before and during the biological era. Besides the availability of biological drugs, other factors played a significant role. The reduced number of patients presenting with complicated severe UC, namely TMC, clearly indicates changes in practice patterns, more timely hospitalization, as well as early recognition of unfavourable prognostic factors. The optimal timing of operation and the strict cooperation between gastroenterologists and surgeons, all contributed to minimizing the fatality rate, as well as reduced the overall need for elective short-term colectomies. Nonetheless urgent colectomy still has an important role in patients with severe complicated UC, as the need for surgery was reduced only to a minor extent, despite the introduction of IFX. Future efforts should be focused on identifying factors characterizing the subgroup of UC patients with rapidly progressive disease. Applying dedicated aggressive medical regimens shall likely improve outcome, and further reduce the mortality rate.

Conflict of interest
None declared.

References

Please cite this article in press as: Clemente V, et al. Short term colectomy rate and mortality for severe ulcerative colitis in the last 40 years. Has something changed? Dig Liver Dis (2016). http://dx.doi.org/10.1016/j.dld.2015.12.014