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Review article

Ileal pouch-anal anastomosis for Crohn's disease. Current status

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Ileal pouch-anal anastomosis has become the standard surgical procedure for the treatment of ulcerative colitis and familial polyposis of the colon. Nevertheless, its use in Crohn's disease patients remains controversial. A review was carried out in order to determine the present scientific evidence on the usefulness of ileal pouch-anal anastomosis in Crohn's disease patients. There are no clinical trials analysing this issue. Scientific evidence is based on case series and retrospective studies. Most authors agree that Crohn's disease remains a contraindication for ileal pouch-anal anastomosis, due to the high rate of complications and pouch failure. Nevertheless, a small group of authors consider ileal pouch-anal anastomosis as a good alternative for selected Crohn's disease patients. Both groups agree that if the pouch can be preserved, functional results are good.

According to our review, current scientific evidence does not recommend ileal pouch-anal anastomosis for Crohn's disease patients.

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Anastomosis ileoanal con reservorio en pacientes con enfermedad de Crohn. Estado actual

R E S U M E N

La colectomía subtotal y la anastomosis ileoanal con reservorio son la técnica de elección para el tratamiento quirúrgico de la colitis ulcerosa. Su utilización en la enfermedad de Crohn (EC) es controvertida. Se realiza una revisión de la literatura para determinar la evidencia científica actual sobre la utilidad de los reservorios ileoanales en los pacientes con EC. No existen ensayos clínicos que aborden específicamente este tema. La evidencia científica actual se basa en series de casos y en estudios retrospectivos. La EC debería seguir siendo una contraindicación para la anastomosis ileoanal con reservorio. Un redu-

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cido número de autores consideran la anastomosis ileoanal con reservorio una buena alternativa para pacientes con EC seleccionados. Ambos grupos coinciden en que los resultados funcionales son buenos.

La evidencia científica actual no recomienda la anastomosis ileoanal con reservorio en pacientes con enfermedad de Crohn.

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Introduction

From the first description in 1978 made by Parks et al,¹ panproctocolectomy with ileoanal pouch surgery (IAP) has become the preferred technique for treating ulcerous colitis (UC) and family colonic polyposis.^{2,3} However, its use in patients with Crohn's disease (CD) continues to be controversial. Consequently, although most of the medical and surgical community considers that CD is an absolute contraindication for performing ileo-anal pouch surgery due to the high rate of complications it involves, some authors have reported good results with this technique in that type of patients.

The alternative to IAP in patients with CD who require a panproctocolectomy is, in most cases, definitive terminal ileostomy, with the unavoidable biopsychosocial consequences this has, in particular in young patients with a high life expectancy. Therefore, it is interesting to examine current scientific evidence to indicate—or contraindicate—this technique in patients with CD. This was the objective of the present study.

Previous experience

The controversy regarding the possibility of performing ileo-anal pouch surgery on patients with CD stems from the first studies that aimed to find different solutions to the same problem. On the one hand we find the authors analyzing ileo-anal or ileo-rectal anastomoses performed, although at that time, without creating a pouch of any kind, and on the other hand we find those who analysed the pouches in terminal ileostomies. Consequently, in 1977 Watts et al⁴ reported good results for ileo-rectal anastomoses in patients with CD and in patients with UC undergoing total colectomy. That same year Flint et al⁵ reported good results in 37 patients with CD but without perianal disease, in whom an elective ileo-rectal anastomosis was performed. Later, Ambrose et al,⁶ from the Birmingham group, assured that ileo-rectal anastomosis is a good alternative for selected patients with CD. However, it should be remembered that despite concluding that it is a good alternative, the re-operating rate after 10 years was almost 50% and the recurrence rate, 64%. Similar conclusions were drawn by Longo et al⁷ considering ileo-anal anastomosis to be a valid alternative when the rectum showed no sign of the disease and the sphincter function was conserved. In turn, Grobler et al⁸ concluded that although the complications rate was high following a restored proctocolectomy, it had good functional results.

In addition, Kock pouches (continent ileostomies) started to be performed for both CD and UC. Nils Kock selected patients in whom the disease was limited to the colon, mostly initially diagnosed with UC, but with the final diagnosis being changed to CD EC.⁹ In this way, 49 of the 280 patients treated with Kock pouches had CD. One patient died during the postoperative period and 27% developed complications. In 8 (16%) patients, the pouch had to be removed, 4 of these due to the recurrence of the disease. Of the remaining 40 patients, a further 17 showed recurrence, 6 in the ileal segment near the pouch, 5 in the pouch only, and 6 in both sites. As the final result, 37 patients (out of 49) had continent ileostomy surgery. With these results, Kock et al⁹ concluded that this procedure should only be used in selected cases of CD. Other authors¹⁰ also reported poor results with this technique and considered that CD is a firm contraindication for this technique.

Situations in which it was decided to perform an IAP on a patient with CD

There are 2 scenarios in which a patient with CD may be a candidate for an IAP. The first is possibly the most frequent in daily practice and the one that most specialists might have encountered at some point, among patients diagnosed initially for UC or indeterminate colitis (IC) and not for CD. Indeed, differential diagnosis between CD and UC is occasionally, extremely difficult to be established, therefore some authors have considered that these two diseases can be distinguished from each other in 10%–15% of cases.¹¹ This would certainly be true in patients with serious intestinal inflammation in whom deep ulcers cross through many layers of the intestinal wall, with or without granuloma, and without any other findings that could permit the CD diagnosis to be confirmed.¹² According to Peyrègne et al,¹³ the difficulty in diagnosing the condition lies in the fact that the presence of granuloma is not constant in CD and can also be seen in other pathologies such as UC and infectious enteritis or in dysfunctional rectums. Ulcerations in the form of fissures can be seen in diverticulitis. Cryptic abscesses show the activity of the disease and are also non-specific. Fulminating colitis is, in addition, a known cause of confusion, due to the discontinuous, transmural inflammation that is produced. In this way, in a considerable percentage of patients diagnosed with CD, this is established, following the anatomopathological study of the surgical resection pieces or after the development of post-surgical complications that are typical of CD, once the IAP is already created. In this case, an undesirable situation arises in which the patient is the carrier

of an IAP which, if the diagnosis had been known previously, would not have been performed.

The second scenario would correspond to the patient already diagnosed with CD in whom, for whatever reason, it is necessary to perform a total colectomy and it is decided, by choice, to restore the digestive tract through IAP.

Clinical symptoms

The clinical symptoms that are most frequent in IAPs performed in CD consist of diarrhoea, abdominal pain, and pelvic discomfort, similar to the symptoms of pouch inflammation and the irritable pouch syndrome that is seen in patients with UC.¹⁴ Shen et al¹⁴ classified the effects of IAPs performed in CD into 3 types: inflammatory CD, fibrostenotic CD, and fistulising CD. According to their analysis, the demographic and clinical characteristics would not be different for all 3 groups, but the predominant symptoms are related with the different phenotypes, so that 92% of patients with inflammatory CD had diarrhoea and/or pain, 64.7% of the fibrostenotic CD patients had blockage symptoms, and 51.6% of the patients with fistulising CD had symptoms associated with fistulous drainage. Fistulising CD was associated in numerical terms with a greater risk of failure of the pouch. The main risk factor for inflammatory CD would be the value obtained from the endoscopy of the afferent loop; for fibrostenotic CD, it would be the value obtained from the endoscopy for the afferent loop and caecal loop and for fistulising CD, the female sex, young age, preoperative diagnosis of IC, and the use of non-steroid anti-inflammatory drugs.¹⁵ According to these authors, as each phenotype is associated with certain risk factors, its etiology will also be different. As a result, the identification and treatments of certain modifiable risk factors could reduce morbidity associated with IAPs performed in CD.

Ettore et al¹⁶ analysed the histological changes produced in the IAP both in CD and UC. Based on their analysis, although pouchitis was the most frequent in patients with CD (56% compared to 28%) the histological changes (including dysplasia) were similar in both diseases. Therefore, although the terminal ileum of patients with CD appears more predisposed to clinical inflammation than in UC patients, there are no histologically-significant differences. However, the perianal lesions and fistules, such as pouch-cutaneous fistules, pouch-bladder, and pouch-vagina fistules in the absence of post-surgical complications such as abscesses, anastomotic failure, or sepsis should indicate the CD diagnosis.¹⁴ The fistules and abscesses may be post-surgical complications of an UC. In general, the CD diagnosis must be considered if the fistules or abscesses develop more than 12 months after performing the IAP and if there are granuloma in the histology.¹⁴ Ulcerated lesions in the afferent loop near the pouch and ulcerated stenosis in the absence of non-steroid anti-inflammatory therapy also point to CD.^{14,17}

Results of the different studies

Based on the 2 scenarios described above, the studies that have evaluated the use of IAP in CD can be divided into 2 types:

a) studies with pre-surgical diagnosis for CD; and b) studies with post-surgical diagnosis for CD.

Studies with preoperative diagnosis for CD

In this type of studies, the work of a small group of authors is included, who have considered the performing of IAP based on choice in patients diagnosed with CD. Among these the group from Lariboisière Hospital in Paris, France, and Queen Elizabeth Hospital in Birmingham, UK, are those with the most experience over the years. In 1996, Panis et al^{18,19} reported the results of 31 patients receiving surgical treatment based on choice between 1985 and 1992. Based on their data, there would be no differences regarding morbidity and mortality or functionality of the pouch comparing UC to CD. Following this, the same authors²⁰ confirmed that the good results were maintained long term, with an average follow-up of 10 years. On the contrary, Mylonakis et al,²¹ compared the results of IAP with those of ileoproctostomies in patients with CD and found higher levels of complications in the IAP, although the functional results after managing to maintain the pouch were good.

The main advantage of this type of study is that the diagnosis of CD can be considered as certain before surgery, thereby reducing the effects of diagnostic error on the results. However, they have serious limitations. The most important is that they have serious limitations. The most important is that they are case series in which the patients were not randomized and, therefore, the decision to use one surgical technique or another is based on the characteristics of each patient, which makes it difficult to make comparisons. Furthermore, the selection criteria used in these studies are normally established arbitrarily, which makes it impossible to analyse the factors related to the greater or lesser functionality of the technique. In the studies conducted by the Paris hospital, and those of the British hospital, the IAP were performed only on patients not suffering from signs of ileal or rectal disease. In other words, the indications for using one or other technique were different, and so it is not possible to establish which patients would be the most suitable candidates for IAP and which would not.

In short, there are no randomised clinical trials that allow IAP to be compared with other techniques in patients with CD. To date, the only available prospective studies are case series that have a small number of patients in whom IAP is recommended only in selected patients, who have no rectal or ileal signs of their disease.

Studies with post-operative diagnosis for CD

Given that, as has been seen, it is relatively frequent that patients diagnosed with UC to be eventually diagnosed with CD—once the colectomy has been performed and therefore, the IAP—, these are the most common studies in literature. In this group of studies, 2 subgroups can, in addition, be established: those making a generic analysis of the risk factors for an IAP failure and who conclude that the CD diagnosis is one of these factors, and those who make a specific analysis of a subgroup of patients diagnosed with CD and compare the results with those of a group diagnosed with UC:

Studies analysing the risk factors of IAPs

In a retrospective study on more than 1000 patients with IAP, Fazio et al³ analysed the risk factors for complications and pouch failure. Although the number of patients finally diagnosed with CD was only 67, of the 34 patients with pouch failure, 17 were diagnosed with CD which is a high failure rate for this group. However, one of the positive conclusions of their study was that the functional and quality of life results were similar for the CD, UC, and IC. In 2003 the same author²² proposed a model for estimating the risk of failure of the IAP in which the diagnosis of CD was included as one of the factors with the greatest effect. According to that analysis, the risk of losing the pouch was 9 times higher in patients with CD in the univariate analysis and 4 times higher in the multivariate analysis on inserting confusion factors related to CD, such as the presence of fistules or perianal sepsis. Foley et al²³ found that the need for an ileostomy following IAP failure was greater in patients with CD when compared to patients with UC (36.8% vs 1.4%). Consequently, a CD diagnosis could significantly predict the subsequent need for an ileostomy following an IAP. Similar results were obtained by Gemlo et al,²⁴ who concluded that poor functional results, pelvic sepsis, and an unsuspected CD diagnosis were the factors more directly related to pouch failure. MacRae et al²⁵ studied 551 patients with IAP and found that the manual anastomoses, tension in the pouch, the use of an ileostomy due to dysfunctionalising and CD diagnosis were associated with a greater risk of pouch failure. Ozuner et al²⁶ did not find that CD was a risk factor for excision, but admitted that the number of patients was too low to obtain significant differences. Paye et al²⁷ analysed only the fistules of the IAP and found that unsuspected CD was one of the risk factors related to its development. Rossi et al²⁸ found that of 75 patients undergoing IAP due to suspected CD, 45% of those with abscesses or fistules and all those with presacral abscesses as a result of anastomotic dehiscence were subsequently diagnosed with CD. In short, according to most of the authors, CD diagnosis following an IAP due to suspected UC is one of the most important risk factors leading to pouch failure.

Studies analysing only patients with CD

Different authors have reported poor results with IAP performed on patients with CD.^{8,13,29-31} The common denominator in all these studies is that IAPs show an excessively high complications rate which contraindicates or at least makes it advisable not to use this technique in patients with CD. However, all the studies coincide in saying that if the pouch is maintained, the functional results are good, and comparable to those obtained in UC. However, not all authors agree with these conclusions. In this way, Hartley et al³² found a lower complications rate (12%), which led them to support the conducting of prospective studies to evaluate the usefulness of IAP in selected CD patients. However, it should be borne in mind that when the diagnosis was based on clinical symptoms, the percentage of complications was higher than when it was based on an anatomic-pathological analysis. As usually occurred too in other studies,^{33,34} the preoperative characteristics, such as active rectal signs, were not predictive of the IAP failure, and

so even though IAP could be offered to selected and especially motivated patients, the lack of criteria to determine the risk factors of failure makes it difficult to take the decision. The only Spanish study on this topic, published by de Oca et al,¹² was unable to demonstrate significant differences with regard to short and long term complications in IAP performed on patients with UC compared to patients with CD. Consequently, they did not find that CD alone was a factor of risk in the excision of the pouch. However, the authors admitted that their results were insufficient to recommend IAP in patients with CD.

The main limitation of this type of study lies in the selection bias that they entail since the IAP is only performed on patients with symptoms or signs of ulcerous colitis and not in all cases of CD. Perhaps the results in selected CD patients who present certain characteristics might be different. In short, most authors agree that the complications rate in IAP performed on patients suspected of having CD who are eventually diagnosed with CD, is too high. However, when the pouch is maintained, the functional results are good.

Explanation of the differences between studies

It is difficult to interpret the important differences in results observed according to the different authors, especially the proportion of patients who required the excision of the IAP in the follow-up process (Table). One possible explanation for these differences could be the variable nature of the criteria established for diagnosing CD. According to Brown et al,³⁴ patients with CD would have much worse prognosis than those with IC and these, in turn, would be worse than UC. In this way, there is a certain consensus of opinion that the results of IAP in patients with IC and UC are good, while the results for CD patients are much worse, as we have seen above. Consequently, it is possible that the studies presenting better results have included patients that other authors would have considered as being IC. Indeed, the complications rates are proportionally higher when the CD diagnosis is based on the presence of epithelioid granuloma.³⁵ In addition, it is not the same for the diagnosis to be based on clinical symptoms than on anatomic-pathological criteria, as confirmed by Hartley et al.³² Furthermore, the presence of chronic pouch inflammation or inflammation that is resistant to treatment has occasionally, been considered as data that is typical of CD not diagnosed before or after surgery, even though Subramani et al³⁶ did not find this association to be true. Similarly, as reported by Goldstein et al³⁷ following the review of 8 surgical resection pieces from patients diagnosed with UC with complications that were typical of CD, the appearance of complications similar to Crohn in the post-surgical period or years after performing an IAP for suspected CD should not modify the initial diagnosis, unless the original pieces are re-examined. Furthermore, Fazio et al³ analysed 2 specific periods of study (1983–1988 vs 1989–1993), and found a higher rate of complications and excision of the pouch in the first period. Similar results were obtained by de Oca et al.¹² Therefore, it would be necessary to also evaluate the degree of specialisation of the surgeon or centre to compare the results. In the same way, we should bear in mind that CD patients

Some of the Studies in Which the Results of IAP in CD Were Analysed

Reference	Year	With CD, No.	Diagnosed With CD	Follow-up, Mean, mo	Excision of IAP, ^a No. (%)	Recommendation to Have IAP
31	1991	25	Post-operative	38.1	8 (32)	In selected cases
11	1991	9	Post-operative	–	4 (44)	No
24	1992	13	Post-operative	–	6 (46)	No
10	1993	8	Post-operative	30	8 (100)	No
3	1995	67	Post-operative	37	17 (25)	No
27	1996	21	Post-operative	–	–	No
29	1996	37	Post-operative	120	17 (46)	No
18	1996	31	Pre-operative	59	2 (6)	In selected cases
25	1997	20	Post-operative	30	11 (55)	No
13	2000	7	Post-operative	84	3 (43)	No
21	2001	23	Pre-operative	122.4	11 (48)	No
20	2001	41	Pre-operative	113 (37)	4 (10)	In selected cases
12	2003	12	Post-operative	76	2 (17)	In selected cases
33	2004	32	Post-operative	153	9 (28)	No
32	2004	60	Post-operative	46	7 (12)	In selected cases
30	2005	52	Post-operative	–	15 (29)	No
34	2005	36	Post-operative	83 (65)	20 (56)	No

CD indicates Crohn's disease; IAP, ileo-anal pouch.

^aIAP dysfunctionalising is also included.

represent a different degree of activity of the disease with a biological behaviour that is different, and therefore when the diagnosis is established due to post-surgical complications, there will be considerable bias, since this would be group with a behaviour that was, *a priori*, more aggressive. On the other hand, given that IAP is not a curative therapy for the underlying disease, since CD must be considered as chronic, the follow-up time could have a certain influence on the results. Finally, in most studies that have analysed the results of IAP in patients with CD, they were compared with those obtained in patients with UC. The results of the IAP in patients with CD are, indisputable, worse than those obtained in patients with UC or family colonic polyposis. However, in an interesting editorial on this subject, Phillips³⁸ affirmed that this situation is like comparing apples to oranges, since they are different diseases. The results of IAP in patients with CD do not seem any worse than those obtained for any other restorative technique in CD. As a result, CD should not be compared to UC, but the different techniques performed for CD among themselves.

In short, these other diagnostic difficulties could have altered the result of some studied, in one way or another, which would justify, at least in part, the differences found.

Treatment of an IAP in a patient with CD

Having analysed the causes and consequences of IAP in patients with CD, the question should finally be raised

regarding what to do when these pouches are already present in a patient with CD, that is, what is the ideal treatment of IAP in patients with CD.

The first concept to be clarified is that, if there are no complications of the pouch and if the functional results in the long term are good, it is not obligatory to convert an IAP into a terminal ileostomy simply because it is not considered a good option in these cases. In other words, once the IAP is present in a patient with CD, it is necessary to make available all the necessary means to preserve its functionality. However, given the low frequency with which IAPs are performed with CD, the data regarding available therapies published in literature are few in number. Consequently, in view of the widespread nature of immunomodulating and biological therapies, most complications must be treated with the dysfunctionalising or excision of the pouch. At present, however, the use of many drugs, including antibiotics, aminosaliclates, corticoids, immunomodulators, and anti-TNF (infliximab, adalimumab, etc),¹⁴ and endoscopic therapies allows the pouch to be preserved in many patients.^{18,39,40} Berrebi et al⁴¹ reported good results with azathioprine in the treatment of recurring CD in 2 ileo-anal pouches. Based on their experience, immunosuppressive treatments would be a good alternative to ileostomy in these patients. Hartley et al³² also demonstrated the beneficial role of immunosuppressors (azathioprine and 6-mercaptopurine) in preventing the recurrence of the disease in patients in

whom the diagnosis had been changed from UC to CD. Ricart et al⁴² reported good results with 1-4 infusions of infliximab at doses of 5 mg/kg for treating complications of IAP in 7 patients diagnosed with CD, even for fistulous lesions, with closing of the paths. Furthermore, fibrostenotic lesions can be treated either with pneumatic dilatations,¹⁴ or stenoplasty.⁴⁰

In short, the recurrence of the disease or the development of complications in IAP patients with CD do not necessarily predict the need for excision or dysfunctionalisation. Although the complications rate is high, it is likely that the pouch functionality can be preserved.

There is insufficient scientific evidence to recommend the performing of ileo-anal pouch surgery in patients with CD subjected to total colectomy. The majority of groups consider that CD is a contraindication for IAP. In addition, the groups with the best results in these situations recommend performing it on selected patients, particularly when the ileum and rectum are not affected. Although the pouch excision or dysfunctionalisation rate is high among patients with CD, in the event of it being possible to maintain the pouch with medical and endoscopic treatment, the functional results are good and comparable to IAP performed for other reasons.

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