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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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Umbilical hernia in patients with liver cirrhosis: A surgical challenge

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Abstract

Umbilical hernia occurs in 20% of the patients with liver cirrhosis complicated with ascites. Due to the enormous intraabdominal pressure secondary to the ascites, umbilical hernia in these patients has a tendency to enlarge rapidly and to complicate. The treatment of umbilical hernia in these patients is a surgical challenge. Ascites control is the mainstay to reduce hernia recurrence and postoperative complications, such as wound infection, evisceration, ascites drainage, and peritonitis. Intermittent paracentesis, temporary peritoneal dialysis catheter or transjugular intrahepatic portosystemic shunt may be necessary to control ascites. Hernia repair is indicated in patients in whom medical treatment is effective in controlling ascites. Patients who have a good perspective to be transplanted within 3-6 mo, herniorrhaphy should be performed during transplantation. Hernia repair with mesh is associated with lower recurrence rate, but with higher surgical site infection when compared to hernia correction with conventional fascial suture. There is no consensus on the best abdominal wall layer in which the mesh should be placed: Onlay, sublay, or underlay. Many studies have demonstrated several advantages of the laparoscopic umbilical herniorrhaphy in cirrhotic patients compared with open surgical treatment.

Key words: Umbilical hernia; Liver transplantation; Liver cirrhosis; Ascites; Hernia repair; Surgical site infection; Mesh; Ascites drainage

Core tip: Umbilical hernia management in cirrhotics is controversial. Indication, timing, and surgical options of herniorrhaphy such as mesh use and laparoscopic

access in these patients remain controversial. This comprehensive review shows that umbilical hernia prevalence is very high in cirrhotic patients with ascites. The etiopathogenesis of umbilical hernia in these patients is discussed in detail. Umbilical hernia management changed markedly in the last decades due to better medical care of cirrhotic patients. Ascites control is the mainstay to avoid surgical complications and recurrence.

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INTRODUCTION

Umbilical hernia is a common condition, with a prevalence of 2% in the general adult population[1]. Hernia incidence in cirrhotics with ascites is 20%[2,3]. Umbilical hernia in these patients has a tendency to enlarge quickly and become symptomatic[4]. Unlike the general population, in which female sex and obesity are risk factors for umbilical hernia, cirrhotic patients who form umbilical hernias are more likely to be men with ascites[2-4].

The treatment of cirrhotic patients with umbilical hernia is controversial[5-8]. In the past, these patients were usually treated expectantly due to the elevated rate of complication and hernia recurrence[5,6]. Nonetheless, expectant management may lead to severe complications, such as hernia incarceration and necrosis and perforation of the overlying skin followed by evisceration, ascites drainage, and peritonitis[7,8]. Many recent studies showed that the results of surgical repair depend on the presence of ascites and liver function grade[9-12]. Elective umbilical herniorrhaphy is safe and effective in most cirrhotic patients in which ascites is adequately controlled[12]. However, it should be avoided in patients in which ascites is not controlled.

At present, there is no high-quality prospective randomized study on management of cirrhotic patients with umbilical hernia to guide decision-making[4]. Indication, timing, and technical aspects of herniorrhaphy in these patients remain controversial[6-10]. Use of mesh and laparoscopic access is also subject to debate[13-15]. Our objective in the present article is to review the management of cirrhotic patients with umbilical hernia, including the indications and results of the surgical treatment. Use of mesh and the laparoscopic access employed in the surgical repair is also reviewed.

PREVALENCE AND ETIOPATHOGENESIS

Umbilical hernia is the third most common abdominal hernia in the general population, after inguinal hernia and incisional hernia[1]. In cirrhotic patients, the prevalence of umbilical hernia is higher[16]. Nearly 20% of cirrhotic patients with ascites have umbilical hernia[2,3]. Prevalence of inguinal hernias is relatively unaffected by ascites[6].

Umbilical hernia etiology in cirrhotics is multifactorial[3-5]. Elevated abdominal pressure secondary to ascites may initiate protrusion of abdominal content through a potential defect at umbilicus[15]. Ascites is possibly the major etiologic factor[6-10]. In cirrhotics, umbilical hernias occur almost exclusively in patients with persistent ascites[11-14]. In addition to increase intra-abdominal pressure, ascites correlates with liver dysfunction. Other important contributory factor is abdominal wall muscle weakness due to hypoalbuminemia and recanalization, dilation and varices formation of the umbilical vein at the umbilicus as a result of portal hypertension[16,17].

In the general population with no co-morbidites, acquired umbilical hernia increases in size very slowly[1]. On the contrary, in individuals with intraabdominal pressure elevated, such as in cirrhotic patients with ascites, umbilical hernia size increases rapidly[6,16]. In addition, ascites is also important in the development of complications in these patients. Ascites may precipitate hernia incarceration of intestine or omentum into the dense fibrous ring at the neck of the hernia[17-20]. Enormous increase of intraabdominal pressure secondary to tense ascites may also cause pressure necrosis and perforation of the overlying skin followed by evisceration, ascites drainage, and peritonitis[19,21].

INDICATIONS AND TIMING OF HERNIA REPAIR

Elective umbilical herniorrhaphy in the general population is the standard treatment[1]. Hernia repair in individuals with no co-morbidities is an operation associated with low complication rate[9]. On the contrary, umbilical herniorrhaphy in cirrhotic patients may cause expressive morbidity, such as wound infection and dehiscence, ascitic drainage through the incision, peritonitis, liver failure, and hernia recurrence[9,10]. Furthermore, presence of umbilical hernia reduces the quality of life[22].

Historically, cirrhotic patients who were subjected to umbilical herniorrhaphy had elevated morbidity and mortality rates that correlated with the severity of liver dysfunction[9,10,16]. The potential complications include decompensation of liver disease, hemorrhage, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, infection, and high hernia recurrence rate[7,8]. Therefore, in the past, surgeons avoided to perform elective umbilical herniorrhaphy in cirrhotic patients despite the operation simplicity[9,23-26].

Umbilical herniorrhaphy in cirrhotics was performed only in patients with hernia complications. Conservative management was the initial option. Nonetheless, expectant management is associated with elevated rate of complications, such as hernia incarceration,

evisceration, ascites drainage, and peritonitis[2,18,21]. Morbidity and mortality are high when umbilical hernia repair is performed on these patients[2,18,27,28].

With improvement in the medical care of cirrhotic patients in the last decades, some studies have showed a significant reduction of umbilical herniorrhaphy complications in these patients[4,6,23]. Marsman *et al*[7] have compared elective surgical repair (n = 17) with expectant treatment (n = 13) in cirrhotic patients with umbilical hernia and ascites. The authors reported that expectant treatment was associated with elevated morbidity and mortality[7]. Hospital admission for hernia incarceration was observed in 10 of 13 patients (77%), of which 6 needed emergency herniorrhaphy[7]. Two patients (15%) who were subjected to expectant treatment died from hernia complications. Conversely, no complications or hernia recurrence was recorded in 12 of 17 patients (71%) who underwent elective herniorrhaphy.

Other studies have also describe superior results and have suggested elective umbilical herniorrhaphy in cirrhotic patients in order to avoid complications associated with conservative management[5,8,9].

Indications and the optimal timing to repair an umbilical hernia in cirrhotic patients remain controversial. Several studies have demonstrated that umbilical hernia repair outcomes in cirrhotics depend on the presence of ascites and liver function grade[6,8]. Child's classification and MELD score have been employed to determine the surgical risk[29-31]. Some other adverse predictors include esophageal varices, age older than 65 years, and albumin level lower than 3.0 g/dL[10].

Most studies have demonstrated that effective treatment of ascites is the essential for umbilical herniorrhaphy in cirrhotic patients[5,7]. In addition, effective ascites control also reduces complications, such as wound infection, evisceration, ascites drainage from the wound, and peritonitis[6].

Medical treatment of ascites with sodium restriction, diuretics, and paracentesis should be the first step in the management. In patients with no significant comorbidities in whom medical treatment is effective in controlling the ascites, umbilical hernia repair is indicated[6].

If medical treatment fails, ascites drainage or shunting is indicated either before or at hernia correction[7-9]. Presently, intermittent paracentesis, temporary peritoneal dialysis catheter or transjugular intrahepatic portosystemic shunt (TIPS) may be employed. These procedures significantly reduce the incidence of hernia recurrence and wound dehiscence[23,32].

Slakey *et al*[32] suggested that the insertion of temporary peritoneal dialysis catheter at the end of umbilical herniorrhaphy in cirrhotic patients was effective in controlling ascites and reducing the complication rate. This approach has some advantages, such as outpatient care during the postoperative period and easy removal of the catheter[32]. However, peritoneal catheters are associated with a high risk of bacterial infections, which significantly increase mortality and should be discouraged[33].

In a survey performed recently with members of the Canadian Hepato-Pancreato-Biliary Society, the preferred choice to ascites treatment in these patients was the use of temporary peritoneal dialysis catheter until wound healing was completed[23]. However, others reported that preoperative TIPS was preferable[27].

Rapid preoperative ascites drainage, either by paracentesis or peritoneal dialysis catheter ascites, is not a risk free procedure, and may cause strangulation of the hernia[10,23,27]. Therefore, it is recommended that ascites drainage should be gradual. Other shuntings, such as portocaval shunt and peritoneovenous shunt, are rarely employed at present. In patients in whom the shunt is effective, surgical treatment of umbilical hernia can be safely performed in most cases[4,34].

In patients in whom ascites control is ineffective, the best alternative is to repair the hernia during the transplant operation, if the patient is on the waiting list for liver transplant[16,35]. Otherwise, surgical repair should not be recommended. Based on literature data, an algorithm for the management of cirrhotic patients with umbilical and ascites is shown in Figure 1.

HERNIA REPAIR IN CANDIDATES TO LIVER TRANSPLANTATION

Liver transplant candidates may underwent umbilical herniorrhaphy during the transplant operation. Patients who have a good perspective to be transplanted within 3-6 mo, herniorrhaphy should be done during transplantation[7]. Postponement of hernia correction is not advisable due to the risk of post-transplant intestinal strangulation of an uncorrected umbilical hernia[6,7,16]. Pressure bandage should be applied carefully on the hernia until transplantation to avoid complications[16].

Some patients with patent large umbilical vein who underwent umbilical hernia repair may need emergency liver transplantation due to acute liver failure[16]. Ligation of a large patent umbilical vein during hernia repair may cause acute liver failure as a result of acute portal vein thrombosis or embolization[16,25].

The umbilical hernia may be repaired at the end of liver transplantation either from inside the abdomen through the same incision employed for the transplantation or through an additional para-umbilical incision[16]. In a retrospective study, de Goede *et al*[16] reported the only study of the literature comparing the two incisions. The recurrence hernia rate was higher in the same incision group than in the separate incision group (40% *vs* 6%)[16]. The number of patients was small in this retrospective study to allow recommendations. At present, the decision of which incision should be used for umbilical hernia repair during liver transplantation is based on the surgeon's experience[7,16].

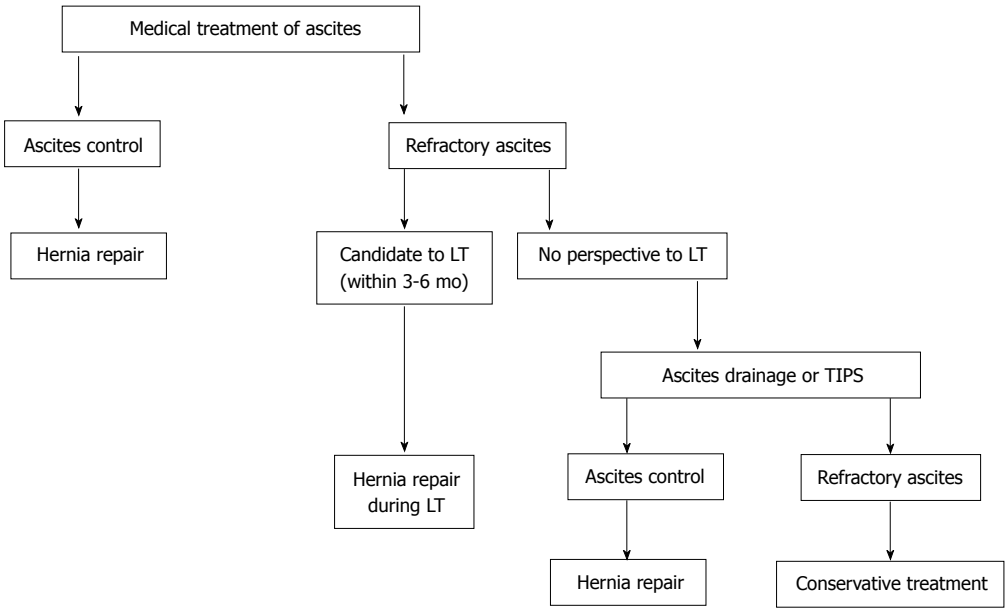

Figure 1 Management of umbilical hernia in patients with liver cirrhosis and ascites. LT: Liver transplantation; TIPS: Transjugular intrahepatic portosystemic shunt.

TREATMENT OF COMPLICATED HERNIA

The rate of complications is high in cirrhotic patients with umbilical hernia and ascites, mainly due to the enormous intraabdominal pressure that enlarges the hernia rapidly[7]. These complications include infection, incarceration, strangulation, and rupture. Non-operative management of these complications is associated with elevated morbidity and mortality[2,7,18,23]. The mortality rate ranges from 60% to 80% following conservative management of ruptured umbilical hernia and 6% to 20% after urgent herniorrhaphy[2,23]. Therefore, complicated umbilical hernia in cirrhotics with ascites should be corrected urgently[2,23].

Initially, the patient should be subjected to appropriate resuscitation with intravenous fluids and antibiotics to prevent or treat ascitic fluid infection[2]. Sterile dressing is indicated in patients with ascitic fluid drainage or cutaneous infection. After patient stabilization, umbilical herniorrhaphy should be done with sutures[2,18]. Mesh should be avoided to decrease the risk of infection[2,18]. Ascites control is important to reduce complications and hernia recurrence[7-9].

HERNIA REPAIR WITH OR WITHOUT MESH

As a result of elevated recurrence rate following the correction of abdominal hernias, including umbilical hernia, in cirrhotic patients, prosthetic mesh repair has been introduced and revolutionized hernia surgery[13,36]. Hernia repair with mesh compared with suture repair reduces hernia recurrence rate, but increases the risk of some complications, including infection, seroma, mesh erosion, and intestinal adhesion, obstruction, and fistula[36-38].

Several studies have demonstrated that elective mesh umbilical herniorrhaphy in cirrhotic patients with ascites is simple, safe, effective, and reduce hernia recurrence markedly[4,7,12]. However, many surgeons are still reluctant to employ mesh for hernia correction in these patients because of the risk of wound complications[12,23]. A significant complication in this group of patients is ascites leakage through the wound, which elevates the possibility of wound and mesh infection, followed by need of mesh removal[36].

In a recent randomized study, 80 cirrhotic patients subjected to umbilical hernia repair were divided into two groups, with a follow-up of 6 to 28 mo[4]. Hernia recurrence rate was lower in the group in which polypropylene mesh was used compared to the group without mesh in which the hernia correction was performed by conventional fascial suture (14.2% *vs* 2.7%)[4]. In this study, surgical site infection was more likely to occur in the mesh group than in the group without mesh, even though no patient needed mesh removal[2]. No mesh exposure or fistulas were observed in this series.

Techniques of mesh placement include onlay, inlay, sublay, and underlay[36,38]. In the onlay repair, the mesh is sutured on external oblique fascia, after dissection of the subcutaneous tissue and closing of the fascia[36]. In the inlay technique, the mesh is placed in the hernia defect and sutured circumferentially to the edges of the fascia[36]. In the sublay procedure, the mesh is inserted in the preperitoneal space or retro-rectus[36]. In the underlay procedure, the mesh is placed intraperitoneally and fixed to the abdominal wall, usually with tackers[36].

The risks of complications are related to the space in which the mesh is placed[36]. In the onlay technique, wound complications are more frequent, such as seroma, hematoma, ascites drainage, and infection of the surgical incision and mesh. This is due to the

Table 1 Advantages of laparoscopic umbilical hernia repair in patients with liver cirrhosis[15,36,37]

Minimally invasive
Tension free repair
Minimal ascites leakage through the wound
Less damage to the large collateral veins
Restricts electrolyte and protein loss due to non-exposure of viscera
Reduced blood loss
Decreased pain
Better aesthetics
Early recovery
Reduced hernia recurrence

extensive detachment of subcutaneous tissue from the fascia, which typically creates a dead space between the mesh fixed on the fascia and the subcutaneous tissue. At present, inlay repair is used only occasionally due to high wound infection and recurrence rates[36].

Wound complications are less common in the sublay and underlay mesh repair techniques because the mesh lies quite deep in the preperitoneal space and intraperitoenally respectively and therefore distant from the subcutaneous tissue and skin[13,36-38]. In the underlay technique, the mesh is in contact with abdominal contents and therefore is subjected to complications, such as intestine adhesion, obstruction, erosion, and fistula[12,13,36,39]. For open surgery, the best abdominal wall layer to place the mesh is still controversial[3,12,14,36]. For laparoscopic umbilical herniorrhaphy, the mesh is routinely inserted intraperitoneally and fixed to the abdominal wall[13,37,38].

At present, countless types and brands of mesh for hernia repair are available. They may be absorbable and permanent synthetic meshes, allograft material, and xenograft material. There is no consensus on the best mesh[12-14,36,37]. The selection is based on several aspects, including type of hernia, presence of infection, location or space of mesh placement, cost and surgeons's preference. The most common mesh used in onlay, inlay, and sublay techniques is the polypropylene mesh[13,37,38]. For intraperitoneal mesh placement (underlay technique), synthetic meshes with different coatings or composite meshes are preferred in order to avoid intestine adherence, occlusion, and fistula[12,14,38].

OPEN OR LAPAROSCOPIC HERNIA REPAIR

The first laparoscopic umbilical herniorrhaphy was described by Sarit *et al*[3] in 2003 in a patient with liver cirrhosis complicated with strangulated hernia. Several studies have documented the advantages of the less invasive laparoscopic access compared with the open surgical approach to treat umbilical hernia in cirrhotic patients[13,15,37]. The laparoscopic umbilical herniorrhaphy is a minimally invasive and tension-free procedure in which a mesh is placed and fixed into the abdominal wall to close the inlet of the hernia[21,40].

By minimizing the access incision, the laparoscopic approach reduces postoperative pain, recovery time, and morbidity[15]. Advantages of laparoscopic umbilical herniorrhaphy in cirrhotics with ascites compared to open surgical treatment are shown in Table 1.

One possible disadvantage of laparoscopic herniorrhaphy is the higher cost, mainly of the equipment and material[23,37,38,41,42]. As mentioned earlier, expansive synthetic meshes with different coatings or composite meshes are needed for laparoscopic hernia repair in order to avoid intestine adherence, occlusion, and fistula. Although, several studies have demonstrated higher costs of laparoscopic abdominal hernia repair, there is no specific study on cost associated with laparoscopic umbilical herniorrhaphy in cirrhotic patients[3,39,41,42]. Considering the postoperative advantages of laparoscopic approach, additional studies are essential to establish the cost-effectiveness of umbilical herniorrhaphy in cirrhotics[23,40].

The laparoscopic approach has been also used for complicated umbilical hernia in cirrhotics. Sarit *et al*[3] performed laparoscopic repair for a strangulated umbilical hernia with refractory ascites successfully by releasing the incarcerated bowel loops and fixing a mesh.

Some technical details are important to be observed at laparoscopic umbilical herniorrhaphy in cirrhotic patients with ascites in order to avoid complications. Oblique insertion of trocars into abdominal wall may avoid postoperative ascitic fistula[3]. Angulation of trocar insertion allows the layers of the abdominal wall to overlap and obstruct potential ascitic drainage. Veres's needle and trocar must be inserted carefully in the left subcostal region to avoid lesion of an enlarged spleen secondary to portal hypertension. In order to decrease the risk of hemorrhage, reduction of incarcerated umbilical hernia contents should be performed meticulously due to the proximity and adherence of umbilical varices[17].

HERNIA RECURRENCE

Umbilical hernia recurrence rate in cirrhotics with ascites ranges from 0% to 40%[3,4,6,7]. Effective ascites management is essential to achieve umbilical hernia repair success as well as to reduce recurrence rate**.** In a recent literature review, McKay *et al*[23] identified only 3 retrospective studies comparing the hernia recurrence in cirrhotic patients with ascites control and without control. When the data of these studies were grouped in a meta-analysis evaluation, the recurrence rate was 45% (22 of 49 patients) in the ascites uncontrolled group and 4% (2 of 47 patients) in the controlled group. The authors concluded that uncontrolled ascites strongly correlates with umbilical hernia recurrence in cirrhotic patients[7,23].

Several studies have reported lower umbilical hernia recurrence following hernia repair with mesh than repair without mesh in cirrhotic patients with ascites[3,4]. In a randomized study with 80 cirrhotic patients who were

subjected to umbilical hernia repair, Ammar[4] reported recurrence rate of 2.7% after hernia repair with polypropylene mesh compared with 14.2% following hernia repair without mesh. However, the rate of wound complications, such as seroma, hematoma, and wound and mesh infection, is higher following umbilical hernia repair with mesh.

In summary, most studies have demonstrated that cirrhotic patients with ascites should have umbilical herniorrhaphy electively after ascites control[12]. When hernia complications occur, such as infection, incarceration, strangulation, and rupture, umbilical herniorrhaphy should be performed urgently. Ascites control is critical to reduce hernia recurrence and postoperative complications. For patients scheduled for liver transplantation, umbilical herniorrhaphy should be done during transplantation.

CONCLUSION

Expectant treatment of cirrhotic patients with umbilical hernia and ascites is associated with elevated rate of complications, such as incarceration, evisceration, ascites drainage and peritonitis. These complications require emergency surgical treatment, which carries expressive morbidity and mortality. Conversely, elective hernia correction may be performed with much less complications and it is therefore advocated. Ascites control is essential to reduce perioperative complications and recurrence. In candidates to liver transplantation, umbilical herniorrhaphy should be performed during transplantation, unless the patient presents with significant symptoms or hernia complication or if the perspective to be transplanted exceeds 3-6 mo. This review has major limitations due to lack of high-quality randomized studies. Most publications on umbilical hernia management in cirrhotic patients are case series or retrospective cohort studies with small number of patients. Definitive answers await large-scale prospective randomized controlled studies.

REFERENCES

1 **Cassie S**, Okrainec A, Saleh F, Quereshy FS, Jackson TD. Laparoscopic versus open elective repair of primary umbilical hernias: short-term outcomes from the American College of Surgeons National Surgery Quality Improvement Program. *Surg Endosc* 2014; **28**: 741-746 [PMID: 24162139 DOI: 10.1007/s00464-013-3252-5]

2 **Chatzizacharias NA**, Bradley JA, Harper S, Butler A, Jah A, Huguet E, Praseedom RK, Allison M, Gibbs P. Successful surgical management of ruptured umbilical hernias in cirrhotic patients. *World J Gastroenterol* 2015; **21**: 3109-3113 [PMID: 25780312 DOI: 10.3748/wjg.v21.i10.3109]

3 **Sarit C**, Eliezer A, Mizrahi S. Minimally invasive repair of recurrent strangulated umbilical hernia in cirrhotic patient with refractory ascites. *Liver Transpl* 2003; **9**: 621-622 [PMID: 12783405 DOI: 10.1053/jlts.2003.50078]

4 **Ammar SA**. Management of complicated umbilical hernias in cirrhotic patients using permanent mesh: randomized clinical trial. *Hernia* 2010; **14**: 35-38 [PMID: 19727551 DOI: 10.1007/s10029-009-0556-4]

5 **Carbonell AM**, Wolfe LG, DeMaria EJ. Poor outcomes in cirrhosis-associated hernia repair: a nationwide cohort study of 32,033 patients. *Hernia* 2005; **9**: 353-357 [PMID: 16132187 DOI: 10.1007/s10029-005-0022-x]

6 **Belghiti J**, Durand F. Abdominal wall hernias in the setting of cirrhosis. *Semin Liver Dis* 1997; **17**: 219-226 [PMID: 9308126 DOI: 10.1055/s-2007-1007199]

7 **Marsman HA**, Heisterkamp J, Halm JA, Tilanus HW, Metselaar HJ, Kazemier G. Management in patients with liver cirrhosis and an umbilical hernia. *Surgery* 2007; **142**: 372-375 [PMID: 17723889 DOI: 10.1016/j.surg.2007.05.006]

8 **Gray SH**, Vick CC, Graham LA, Finan KR, Neumayer LA, Hawn MT. Umbilical herniorrhapy in cirrhosis: improved outcomes with elective repair. *J Gastrointest Surg* 2008; **12**: 675-681 [PMID: 18270782 DOI: 10.1007/s11605-008-0496-9]

9 **Choi SB**, Hong KD, Lee JS, Han HJ, Kim WB, Song TJ, Suh SO, Kim YC, Choi SY. Management of umbilical hernia complicated with liver cirrhosis: an advocate of early and elective herniorrhaphy. *Dig Liver Dis* 2011; **43**: 991-995 [PMID: 21872542 DOI: 10.1016/j.dld.2011.07.015]

10 **Cho SW**, Bhayani N, Newell P, Cassera MA, Hammill CW, Wolf RF, Hansen PD. Umbilical hernia repair in patients with signs of portal hypertension: surgical outcome and predictors of mortality. *Arch Surg* 2012; **147**: 864-869 [PMID: 22987183 DOI: 10.1001/archsurg.2012.1663]

11 **Saleh F**, Okrainec A, Cleary SP, Jackson TD. Management of umbilical hernias in patients with ascites: development of a nomogram to predict mortality. *Am J Surg* 2015; **209**: 302-307 [PMID: 25066022 DOI: 10.1016/j.amjsurg.2014.04.013]

12 **Eker HH**, van Ramshorst GH, de Goede B, Tilanus HW, Metselaar HJ, de Man RA, Lange JF, Kazemier G. A prospective study on elective umbilical hernia repair in patients with liver cirrhosis and ascites. *Surgery* 2011; **150**: 542-546 [PMID: 21621237 DOI: 10.1016/j.surg.2011.02.026]

13 **Hassan AM**, Salama AF, Hamdy H, Elsebae MM, Abdelaziz AM, Elzayat WA. Outcome of sublay mesh repair in non-complicated umbilical hernia with liver cirrhosis and ascites. *Int J Surg* 2014; **12**: 181-185 [PMID: 24378913 DOI: 10.1016/j.ijsu.2013.12.009]

14 **Gurită RE**, Popa F, Bălălău C, Scăunasu RV. Umbilical hernia alloplastic dual-mesh treatment in cirrhotic patients. *J Med Life* 2013; **6**: 99-102 [PMID: 23599831]

15 **Belli G**, D'Agostino A, Fantini C, Cioffi L, Belli A, Russolillo N, Langella S. Laparoscopic incisional and umbilical hernia repair in cirrhotic patients. *Surg Laparosc Endosc Percutan Tech* 2006; **16**: 330-333 [PMID: 17057574 DOI: 10.1097/01.sle.0000213745.15773.c1]

16 **de Goede B**, van Kempen BJ, Polak WG, de Knegt RJ, Schouten JN, Lange JF, Tilanus HW, Metselaar HJ, Kazemier G. Umbilical hernia management during liver transplantation. *Hernia* 2013; **17**: 515-519 [PMID: 23793929 DOI: 10.1007/s10029-013-1131-6]

17 **McAlister V**. Management of umbilical hernia in patients with advanced liver disease. *Liver Transpl* 2003; **9**: 623-625 [PMID: 12783406 DOI: 10.1053/jlts.2003.50121]

18 **Kirkpatrick S**, Schubert T. Umbilical hernia rupture in cirrhotics with ascites. *Dig Dis Sci* 1988; **33**: 762-765 [PMID: 3286159 DOI: 10.1007/BF01540442]

19 **Krawczyk M**, Mikneviciute J, Schürholz H. Incarcerated Umbilical Hernia After Colonoscopy in a Cirrhotic Patient. *Am J Med* 2015; **128**: e13-e14 [PMID: 25656110 DOI: 10.1016/j.amjmed.2014.12.028]

20 **Hammad HT**, Chennamaneni V, Ahmad DS, Esmadi M. Strangulated umbilical hernia after esophagogastroduodenoscopy in a patient with liver cirrhosis and ascites. *Endoscopy* 2014; **46** Suppl 1 UCTN: E247 [PMID: 24853441 DOI: 10.1055/s-0034-136488]

21 **Yu BC**, Chung M, Lee G. The repair of umbilical hernia in cirrhotic patients: 18 consecutive case series in a single institute. *Ann Surg Treat Res* 2015; **89**: 87-91 [PMID: 26236698 DOI: 10.4174/astr.2015.89.2.87]

22 **Andraus W**, Pinheiro RS, Lai Q, Haddad LB, Nacif LS, D'Albuquerque LA, Lerut J. Abdominal wall hernia in cirrhotic patients: emergency surgery results in higher morbidity and mortality. *BMC Surg* 2015; **15**: 65 [PMID: 25990110 DOI: 10.1186/s12893-015-

0052-y]
23 **McKay A**, Dixon E, Bathe O, Sutherland F. Umbilical hernia repair in the presence of cirrhosis and ascites: results of a survey and review of the literature. *Hernia* 2009; **13**: 461-468 [PMID: 19652907 DOI: 10.1007/s10029-009-0535-9]
24 **de la Peña CG**, Fakih F, Marquez R, Dominguez-Adame E, Garcia F, Medina J. Umbilical herniorrhaphy in cirrhotic patients: a safe approach. *Eur J Surg* 2000; **166**: 415-416 [PMID: 10881956 DOI: 10.1080/110241500750009005]
25 **Reissfelder C**, Radeleff B, Mehrabi A, Rahbari NN, Weitz J, Büchler MW, Schmidt J, Schemmer P. Emergency liver transplantation after umbilical hernia repair: a case report. *Transplant Proc* 2009; **41**: 4428-4430 [PMID: 20005416 DOI: 10.1016/j.transproceed.2009.08.068]
26 **Banu P**, Popa F, Constantin VD, Bălălău C, Nistor M. Prognosis elements in surgical treatment of complicated umbilical hernia in patients with liver cirrhosis. *J Med Life* 2013; **6**: 278-282 [PMID: 24155783]
27 **Telem DA**, Schiano T, Divino CM. Complicated hernia presentation in patients with advanced cirrhosis and refractory ascites: management and outcome. *Surgery* 2010; **148**: 538-543 [PMID: 20346479 DOI: 10.1016/j.surg.2010.01.002]
28 **Triantos CK**, Kehagias I, Nikolopoulou V, Burroughs AK. Surgical repair of umbilical hernias in cirrhosis with ascites. *Am J Med Sci* 2011; **341**: 222-226 [PMID: 20890175 DOI: 10.1097/MAJ.0b013e3181f31932]
29 **Bhangui P**, Laurent A, Amathieu R, Azoulay D. Assessment of risk for non-hepatic surgery in cirrhotic patients. *J Hepatol* 2012; **57**: 874-884 [PMID: 22634123 DOI: 10.1016/j.jhep.2012.03.037]
30 **Neeff H**, Mariaskin D, Spangenberg HC, Hopt UT, Makowiec F. Perioperative mortality after non-hepatic general surgery in patients with liver cirrhosis: an analysis of 138 operations in the 2000s using Child and MELD scores. *J Gastrointest Surg* 2011; **15**: 1-11 [PMID: 21061184 DOI: 10.1007/s11605-010-1366-9]
31 **Park JK**, Lee SH, Yoon WJ, Lee JK, Park SC, Park BJ, Jung YJ, Kim BG, Yoon JH, Kim CY, Ha J, Park KJ, Kim YJ. Evaluation of hernia repair operation in Child-Turcotte-Pugh class C cirrhosis and refractory ascites. *J Gastroenterol Hepatol* 2007; **22**: 377-382 [PMID: 17295770 DOI: 10.1111/j.1440-1746.2006.04458.x]
32 **Slakey DP**, Benz CC, Joshi S, Regenstein FG, Florman SS. Umbilical hernia repair in cirrhotic patients: utility of temporary peritoneal dialysis catheter. *Am Surg* 2005; **71**: 58-61 [PMID: 15757059]
33 **Kathpalia P**, Bhatia A, Robertazzi S, Ahn J, Cohen SM, Sontag S, Luke A, Durazo-Arvizu R, Pillai AA. Indwelling peritoneal catheters in patients with cirrhosis and refractory ascites. *Intern Med J* 2015; **45**: 1026-1031 [PMID: 26122531 DOI: 10.1111/imj.12843]
34 **Silva FD**, Andraus W, Pinheiro RS, Arantes-Junior RM, Lemes MP, Ducatti Lde S, D'albuquerque LA. Abdominal and inguinal hernia in cirrhotic patients: what's the best approach? *Arq Bras Cir Dig* 2012; **25**: 52-55 [PMID: 22569980]
35 **Mateo R**, Stapfer M, Sher L, Selby R, Genyk Y. Intraoperative umbilical herniorrhaphy during liver transplantation. *Surgery* 2008; **143**: 451-452 [PMID: 18291269 DOI: 10.1016/j.surg.2007.10.019]
36 **Holihan JL**, Nguyen DH, Nguyen MT, Mo J, Kao LS, Liang MK. Mesh Location in Open Ventral Hernia Repair: A Systematic Review and Network Meta-analysis. *World J Surg* 2016; **40**: 89-99 [PMID: 26423675 DOI: 10.1007/s00268-015-3252-9]
37 **Umemura A**, Suto T, Sasaki A, Fujita T, Endo F, Wakabayashi G. Laparoscopic umbilical hernia repair in a cirrhotic patient with a peritoneovenous shunt. *Asian J Endosc Surg* 2015; **8**: 212-215 [PMID: 25418015 DOI: 10.1111/ases.12160]
38 **Vorst AL**, Kaoutzanis C, Carbonell AM, Franz MG. Evolution and advances in laparoscopic ventral and incisional hernia repair. *World J Gastrointest Surg* 2015; **7**: 293-305 [PMID: 26649152 DOI: 10.4240/wjgs.v7.i11.293]
39 **Fernández Lobato R**, Ruiz de Adana Belbel JC, Angulo Morales F, García Septiem J, Marín Lucas FJ, Limones Esteban M. Cost-benefit analysis comparing laparoscopic and open ventral hernia repair. *Cir Esp* 2014; **92**: 553-560 [PMID: 24054792 DOI: 10.1016/j.ciresp.2013.04.012]
40 **Silecchia G**, Campanile FC, Sanchez L, Ceccarelli G, Antinori A, Ansaloni L, Olmi S, Ferrari GC, Cuccurullo D, Baccari P, Agresta F, Vettoretto N, Piccoli M. Laparoscopic ventral/incisional hernia repair: updated Consensus Development Conference based guidelines [corrected]. *Surg Endosc* 2015; **29**: 2463-2484 [PMID: 26139480 DOI: 10.1007/s00464-015-4293-8]
41 **Colavita PD**, Tsirline VB, Walters AL, Lincourt AE, Belyansky I, Heniford BT. Laparoscopic versus open hernia repair: outcomes and sociodemographic utilization results from the nationwide inpatient sample. *Surg Endosc* 2013; **27**: 109-117 [PMID: 22733198 DOI: 10.1007/s00464-012-2432-z]
42 **Tiwari MM**, Reynoso JF, High R, Tsang AW, Oleynikov D. Safety, efficacy, and cost-effectiveness of common laparoscopic procedures. *Surg Endosc* 2011; **25**: 1127-1135 [PMID: 20927546 DOI: 10.1007/s00464-010-1328-z]

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Chronic haemorrhagic radiation proctitis: A review

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Abstract

Chronic haemorrhagic radiation proctitis (CHRP) is a difficult problem faced by the patients following radiation for pelvic malignancy. There is no standard treatment for this condition, but many methods of treatment are available. The aim of this study was to review the literature to see whether there is an improvement in the available evidence in comparison with previously published systematic reviews in treating patients with CHRP. The PubMed/Medline database and Google Scholar search was selectively searched. Studies, which treated patients with rectal bleeding due to chronic radiation proctitis or CHRP, were included. Seventy studies were finally selected out of which 14 were randomized controlled clinical trials. Though these studies could not be compared, it could be seen that there was an improvement in the methodology of the studies. There was an objective assessment of symptoms, signs and an objective assessment of outcomes. But, still, there were only a few studies that looked into the quality of life following treatment of CHRP. To increase recruitment to trials, a national registry of cases with established late radiation toxicity would facilitate the further improvement of such studies. Some of the conclusions that could be reached based on the available evidence are 4% formalin should be the first line treatment for patients with CHRP. Formalin and argon plasma coagulation (APC) are equally effective, but formalin is better for severe disease. Refractory patients, not responding to formalin or APC, need to be referred for hyperbaric oxygen therapy or surgery. Radio-frequency ablation is a promising modality that needs to be studied further in randomized trials.

Key words: Radiotherapy; Complications; Systematic review; Proctitis; Formalin

Core tip: The aim of this study was to review the literature to see whether there is an improvement in the available evidence in comparison with the previously published systematic reviews in treating patients with chronic haemorrhagic radiation proctitis (CHRP). The PubMed/Medline database and Google Scholar search was selectively searched. Seventy studies were finally

selected out of which 14 were randomized controlled clinical trials. It could be seen that there was an improvement of the methodology of the studies though they were not comparable. Based on the available evidence, 4% formalin should be the first line treatment for patients with CHRP.

Nelamangala Ramakrishnaiah VP, Krishnamachari S. Chronic haemorrhagic radiation proctitis: A review. *World J Gastrointest Surg* 2016; 8(7): 483-491 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i7/483.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i7.483

INTRODUCTION

One to five percent of patients who receive radiotherapy as adjuvant or neoadjuvant therapy for pelvic malignancy will develop chronic haemorrhagic radiation proctitis (CHRP). In one of the recently published series, it was noted that 1319 patients received radiation for carcinoma of cervix over a period of 22 mo and 124 similar patients during the same period needed treatment for CHRP in the same centre[1]. The meaning of the above sentence shows the magnitude of the problem of CHRP. Newer methods of radiotherapy like three-dimensional conformal radiation therapy and intensity-modulated radiation therapy can use higher doses of radiation to the target tissues with less exposure to adjacent normal tissues. Protons and neutrons, so-called particle radiation, are also being tested but the long-term outcomes of these modalities are not known, and these are expensive. The use of brachytherapy is also found to be associated with fewer complications. Thus, the incidence of CHRP is related to the dose of radiation, the area of exposure, methods of delivery, the use of cytoprotective agents and other factors[2].

Because the rectum has a fixed position in the pelvis, it becomes more susceptible to radiation injury. Acute radiation injury of rectum occurs within three months of starting radiotherapy. It is an inflammatory process of rectal mucosa with a loss of microvilli, oedema, and ulceration. It is self-limiting and manifests as abdominal pain, tenesmus, diarrhoea, incontinence and urgency and resolves within three months[3]. Unlike acute radiation proctitis, chronic radiation proctitis takes a period of 3 mo after pelvic radiation, but usual median time is 8-12 mo. It can also continue from acute phase[3]. It is due to obliterative endarteritis, submucosal fibrosis, and neo-vascularization (Figure 1). Chronic radiation proctitis can present with rectal bleeding, tenesmus, mucus discharge, diarrhoea, incontinence, and urgency. It may be asymptomatic also. The diagnosis of radiation proctitis should be suspected if a patient presents with the above mentioned symptoms and gives a history of pelvic radiation. The diagnosis is confirmed by sigmoidoscopy or colonoscopy that shows pale, friable mucosa with telangiectasia. Rectovaginal, recto-urethral, recto-vesicular fistulizing disease is a late-presenting sign. There is no role of biopsy to confirm the diagnosis since it may produce complications.

There is no standard treatment for CHRP. However many treatments are available like amino salicylates, butyric acid enema, steroid enemas, formalin, argon plasma coagulation (APC), hyperbaric oxygen, radiofrequency ablation and even surgical therapy. The outcome of any of these medical and surgical treatment can be disappointing[1]. There are not many good-quality placebo-controlled trials.

In this study, our aim was to review the literature to see whether there is an improvement in the available evidence in comparison with previously published systematic reviews in treating patients with CHRP. The PubMed/Medline literature database was selectively searched for articles with the keywords "Proctitis/drug therapy"(Mesh) or "Proctitis/radiotherapy"(Mesh) or "Proctitis/surgery"(Mesh) and "radiotherapy", "Management of CHRP" "Related Review articles". In addition Google search and Google Scholar search was also made using key words "Radiation proctitis" "Formalin" "Endoscopic therapy" "APC" "Radiofrequency ablation" "cryotherapy" "Hyperbaric oxygen therapy" and "surgery". The literature search was mostly limited to articles in English and human patients. No limitations for the year of publication were applied. All the studies that treated patients with rectal bleeding due to chronic radiation proctitis or CHRP were included in the review. Studies of patients treating acute radiation proctitis were excluded.

We could find 142 articles in total. After removing the duplicates and studies on acute radiation proctitis, there were about 86 articles. Out of these 86, 16 were further excluded because of various reasons such as anecdotal studies. Various studies that were found to be relevant are summarized below. Importance was given to randomized controlled clinical trials.

STUDIES USING ANTI-INFLAMMATORY DRUGS, STEROIDS, SUCRALFATE AND PENTOSAN POLYPSULPHATE

Sulfasalazine or 5-aminosalicylates, steroids are the drugs used initially for treating CHRP. Their mechanism of action is by inhibition of prostaglandin synthesis. It may also be due to inhibition of folate-dependent enzymes[4]. Sucralfate stimulates epithelial healing and forms a protective barrier[5]. Sucralfate is shown to be better than anti-inflammatory agents[6]. Pentosan polysulphate is similar to sucralfate. There are more than seven to eight publications using these drugs.

In a prospective double-blind, randomized controlled trial involving 37 consecutive patients with radiation-induced proctosigmoiditis[6], there were 36 females treated for cervical cancer and one male treated for prostate cancer. The mean duration after completion

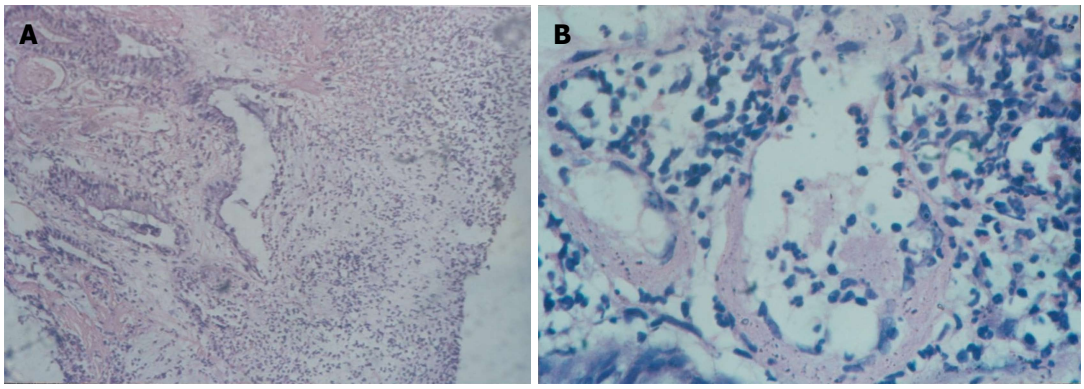

Figure 1 Chronic radiation proctitis. A: Chronic radiation proctitis (low power view). This picture shows the mucosa with severe oedema, non-specific inflammation, lymphocytosis, hyalinization in the stroma and fibrin thrombi in the postcapillary venules (Hematoxylin and Eosin stain, 10 ×); B: Chronic radiation proctitis (High power view). This picture shows two veins in the lamina propria, one with patchy occlusive fibrin thrombus. The wall shows thickening and hyalinization. A dense non-specific inflammation including few eosinophils also seen (Hematoxylin and Eosin stain, 40 ×).

of the radiotherapy was 8.3 mo. These patients were randomized to receive either 3 g oral sulfasalazine plus 20 mg twice daily of rectal prednisolone enemas (group Ⅰ, *n* = 18) or 2 g of rectal sucralfate enema plus oral placebo (group Ⅱ, *n* = 19) for four weeks. These two groups were comparable with respect to demography, clinical symptoms and endoscopic staging of the disease. Patients in Sucralfate enema showed a better clinical response although endoscopically the response was not statistically significant. Follow-up was limited to 4 wk.

Rougier *et al*[7,8], in their randomized trial, compared betamethasone enema (5 mg bd) with hydrocortisone mousse (90 mg bd) and concluded that hydrocortisone group had a better outcome. There were 32 patients with CHRP in this study. The outcomes used were bowel activity, tenesmus, rectal bleeding and endoscopic grading. Follow-up was limited to 4 wk.

In another randomized study by Cavcić *et al*[9], compared combination of oral metronidazole (400 mg tds), mesalamine (1 g tds) and rectal betamethasone to oral mesalamine and rectal betamethasone and found that the rectal bleeding and ulcers were significantly lower in the metronidazole group. In this study, there were sixty patients randomized into either group. The efficacy of metronidazole was assessed on the basis of rectal bleeding, diarrhoea and proctosigmoidoscopy in all patients. The follow-up was up to 12 mo. Grigsby *et al*[10] prospectively showed the benefit of oral pentosan polysulphate given for a period of 1 year in 13 patients.

STUDIES USING SHORT-CHAIN FATTY ACID ENEMAS

Short-chain fatty acids (SCFA) stimulate the growth of colonic mucosa. The vasodilatation effect may improve the blood flow of colonic mucosa[11]. Butyric acid is the main SCFA. There are more than six studies using SCFA. Many of them are case series.

Two randomized studies showed non-significant improvement of symptoms and signs but both the studies were underpowered[12,13]. Talley *et al*[12] in their randomized double-blind placebo-controlled cross over trial of 15 patients treated one group with the butyric acid enema and another group with normal saline placebo. Symptoms score, endoscopic scores and even histology were compared.

Similarly, Pinto *et al*[13] in their randomized prospective double blind controlled trial of 19 patients treated one group with SCFA enema and another group with placebo. In this study apart from symptoms and endoscopic features, biopsies for mucosal DNA and protein content were also measured. Patients were followed up to 6 mo.

Though we were treating patients with CHRP in our institute since 1985, study on chronic haemorrhagic proctitis were started in 1999. The first study on CHRP in our institute, done by Senthil Kumar *et al*[14] in 2001, compared sucralfate-steroid enema (25 mg of prednisolone and 1 g of sucralfate twice daily for 14 d) with butyric acid retention enema (60 mL containing 40 mmol of butyric acid twice daily for 14 d) in a double-blind randomized controlled trial. There were thirty patients randomly allocated. They were followed up to 4 wk. Outcomes were measured by the improvement in the colonoscopic grading of severity and clinical symptoms. Histopathological improvements were also compared by taking the biopsy before and after treatment. The conclusion was that both the methods of treatment were equally effective since there was relief of symptoms of radiation proctitis in both the methods of treatment without improvements in endoscopic scores or histology. However, the sucralfate-steroid enema was easier to prepare[14]. No toxicities were reported in any of these studies.

STUDIES USING FORMALIN THERAPY

Formalin scleroses and seals fragile neovasculature in tissues damaged due to radiation and prevents further bleeding. In 1986, Rubinstein was the first

to use formalin for a CHRP patient to get a good response[15]. Following this, there are several reports in the literature[16-30]. But the majority are retrospective in nature, a few are prospective studies. The technique and the concentration of formalin used in these studies also differ. The two main methods of using it are 4% solution as irrigation or as soaks. There are reports of using 10% solution of formalin also[31]. There are four Randomized trials using formalin for CHRP.

Ours is one of the first published randomized trial comparing the efficacy of the 4% formalin dab with Sucralfate-steroid retention enema (100 mg of prednisolone and 1 g sucralfate in 100 mL of normal saline twice daily for 14 d)[1]. In this study, 102 patients were randomly allocated to either of the treatment arms. This study objectively assessed the symptoms scores using the radiation proctopathy system assessment scale (RPSAS) and also the sigmoidoscopic grade (Modified Chi grading) before and after treatment and found that Formalin dab is superior to sucralfate-steroid enema in treating CHRP involving only the rectum. It was also observed that a single session of formalin dab can effectively treat CHRP in 90% of the patients, and multiple sessions could effectively treat 99% of the patients whereas sucralfate-steroid enema was effective only in 75% of patients. These patients were followed up to 9 mo. There was no complications or toxicity.

Following this Yeoh *et al*[32] showed in their randomized study that APC and topical formalin had comparable efficacy in the durable control of rectal bleeding associated with chronic radiation proctitis but had no beneficial effect on anorectal dysfunction. In this study thirty patients were randomized into each group. Anorectal symptoms, (modified LENT-SOMA questionnaire) anorectal manometry and anorectal morphology by endorectal ultrasound were assessed before and after treatment.

Guo *et al*[33] in their randomized trial showed that 10% formalin is associated with complications and 4% formalin should be the choice for treating CHRP. In this study 122 patients were randomized into 4% or 10% formalin application. Outcomes were compared with symptoms score and rectoscope scores. Follow-up was up to 1 year. Wong *et al*[34] from their prospective database, after a decade of experience of treating patients with radiation proctitis, have shown that formalin is more effective than APC in treating patients with CHRP. APC has the potential to complement topical formalin application and can be used to treat the proximal and distal rectum concurrently.

The contrary report has been published by Alfadhil *et al*[35] in their retrospective comparative study of 22 patients who received formalin application or APC. Improvement in Hb% was used to assess the outcome. The severity of the proctitis was not assessed before the treatment. The lag time between radiation and endoscopic treatment was not known. The study was underpowered, and the groups were not comparable. The details of the adverse events not mentioned. They concluded that APC is more effective than formalin and has less adverse effects.

Sahakitrungruang *et al*[36] in their randomized controlled trial comparing colonic irrigation with oral antibiotics administration *vs* 4% formalin application for treatment of CHRP have shown that the former method is better than 4% formalin application. Fifty patients were randomly allocated to each arm. Daily self-administered colonic irrigation of 1 L tap water and a 1-wk period of oral antibiotics-ciprofloxacin and metronidazole were given in one arm. Four percent formalin application for 3 min was done in another arm. Patient's satisfaction was surveyed. The limitation was that the study was a 2-armed design without a crossover trial. Hence, it could not illustrate whether the antibiotics and irrigation were equally important. Some of the adverse events noted in the literature regarding the use of formalin for CHRP are the rectal stricture, worsening of incontinence, anococcygeal pain, and formalin colitis[24,30].

STUDIES USING THERMAL COAGULATION THERAPY

Endoscopic coagulation with a variety of devices has been reported to be effective for CHRP[7]. The technique involves coagulation of a bleeding point rather than the entire friable mucosa. Several treatment sessions are often required[7]. The modalities include heater probe, bipolar Electrocoagulation, neodymium:yttrium-aluminium-garnet (Nd:YAG) laser, potassium titanyl phosphate (KTP) laser, argon laser and APC. Simple heater probe and APC are preferred for their better safety profile[37].

Both the heater probe and bipolar cautery are contact probes. The heater probe has a Teflon-coated heating element at its tip that delivers standardized energy over set times. Bipolar electrocautery probe has a pair of electrodes at its tip through which current is passed using the tissue for conduction[38]. Jensen *et al*[39] in his randomized study showed that 21 patients treated either with a heater probe, or bipolar cautery showed benefits without much difference between the two modalities[39]. A mean of four sessions was needed in each arm during treatment in this study. Patients were followed up to one year. The increase in haematocrit, endoscopic resolution, and patient satisfaction were compared. No complications were noted.

Nd:YAG laser is the first endoscopic laser used for treating CHRP. Some of the complications reported with this are transmural necrosis, fibrosis, necrosis, stricture formation and recto-vaginal fistula. Nd:YAG laser use for CHRP has declined due to several reasons, firstly its cost; second, the need to aim directly at telangiectasias and the possibility of severe endoscopic damage if the laser strikes the endoscope in retroflection[40]. Taylor *et al*[41] used KTP laser for treating 26 patients

with bleeding secondary to CHRP using 4-10 W and a median of two sessions. They reported a symptomatic improvement in 65% patients while there was no change in 7 (30%), and symptom like hematochezia increased in 1 (5%). Similarly, there are only case series using argon laser for treating CHRP.

There are more than 15 published reports of APC for CHRP. Many are retrospective studies, and some of them are prospective case series. Many of the series report unsuccessful medical treatment before going for APC. In APC bipolar diathermy current is applied using inert argon gas as a conducting medium. It can be applied tangentially and radially.

Karamanolis *et al*[42] showed in their prospective study treating more than 56 patients, that APC was successful in all patients with mild and in almost all patients with moderate CHRP. In contrast, APC failed in 50% of patients, wherever the presence of severe mucosal damage was present. The grading of severity was based on endoscopic criteria taking into consideration telangiectasia distribution and surface area involved. For APC application, a 2.3 mm diameter front firing APC probe inserted through the working channel of the flexible sigmoidoscope was used. The argon flow rate and the electrical power were set at 2 L/min and 40 W, respectively. Patients were followed up for a mean of 17 mo. Patients required 1-2 sessions of APC for mild proctitis while patients with moderately to the severe form required a statistically significantly higher number of APC sessions. In cases of severe and diffuse involvement of the rectum, multiple treatments sessions are required, and success is less certain as shown by other reports also[43-51]. In many of these series, the response is objectively scored using bleeding severity score, haematological parameters, and endoscopic scores.

Chruscielewska-Kiliszek *et al*[52] in their randomized, double-blind trial comparing oral sucralfate or placebo following APC for CHRP have shown that additional sucralfate treatment after APC did not influence the clinical or endoscopic outcomes. One hundred and seventeen patients completed the treatment protocol, 57 in the sucralfate group and 60 in the placebo group. Patients were graded clinically and endoscopically according to the Chutkan and Gilinski scales before and at 8 and 16 wk after initial APC treatment (1.5-2 L/min, 25-40 W) and after 52 wk (clinical only)[52]. Complications (1%-15%) following APC, such as pain, ulceration, perforation, explosion, extensive necrosis and rectal stricture have been cited in the literature[42].

STUDIES USING RADIO-FREQUENCY ABLATION

There are more than five reports of case series and retrospective studies using radio-frequency ablation (RFA) for CHRP. Many case series have shown, using BARRx Halo90 electrode catheter that was fit on the distal end of the flexible sigmoidoscope, an energy density of 12 J/cm^2 at a power density of 40 W/cm^2, hemostasis could be obtained after 1 to 2 sessions[53-56].

Several benefits RFA have been claimed, these include squamous re-epithelialization, lack of stricturing and ulceration. Using RFA much broader area of tissue can be treated simultaneously compared to the point by point approach by other methods[37]. The radio-frequency unit is mobile and can be used in different rooms of an endoscopy unit. Zhou *et al*[54] have used real-time endoscopic optical coherence tomography (EOCT) to visualize epithelialization and subsurface tissue microvasculature pre- and post-treatment RFA in their case series and have shown the potential of EOCT for follow-up assessment of endoscopic therapies.

STUDIES USING CRYOABLATION

Cryoablation is similar to APC and involves the non-contact application of liquid nitrogen or carbon-dioxide to tissues for superficial ablation. It is possible to treat a larger surface area like in RFA. Its effect is due to ischemic necrosis which can be immediate or delayed.

There are only case series of 20 patients. During cryoablation, a decompressive rectal tube has to be inserted because of the risk of over insufflation and perforation. Cryotherapy units are less mobile. Unlike in Radiofrequency ablation, the depth of tissue penetration may be more here. This may lead to strictures. However, colonic lavage is not necessary since there is no risk of explosion. The number of required sessions range from one to four[57-59].

STUDIES USING HYPERBARIC OXYGEN THERAPY

There are more than 12 published studies using hyperbaric oxygen therapy (HBOT) for CHRP**.** New reports have started appearing in the literature regarding the efficacy of HBOT.

Clark *et al*[60] in their randomized controlled double-blind crossover trial (150 patients) with a long-term follow-up, up to 5 years, showed that in patients with refractory CHRP, HBOT had a significant healing response. Primary outcome measures involved were the late effect in normal tissue-subjective, objective, management, analytic (SOMA-LENT) score and standardized clinical assessment. The secondary outcome was the change in the quality of life[60].

In one of the largest Australasian study using HBOT for chronic radiation injuries, Tahir *et al*[61] showed a clinical response rate for CHRP of 95%, where around half of the cases had a durable major response, with some patients experiencing symptom relief lasting as long as seven years.

At pressure greater than atmospheric pressure and using 100% oxygen, HBOT has an angiogenic effect and has been shown to cause an eight to nine-fold increase

in the vascular density of soft tissues over air-breathing controls[7]. HBO acts to stimulate collagen formation and re-epithelialization. There is no uniformity in the methods of treatment using HBOT[42,61-65]. Although it can be perceived from the studies that HBOT is useful in refractory radiation proctitis, there is marked variation between the studies. There are no major adverse effects. Minor adverse event recorded is transient aural barotrauma. The reported number of HBOT sessions for a successful treatment range from 12 to 90. The cost of HBOT is high, and hence, it is not widely applicable.

Other interventions

Oxidative stress is thought to be one of the mechanisms in the development of chronic radiation proctitis and antioxidants have been used to treat CHRP. Use of vitamin C and E have been reported. Kennedy *et al*[66] treated twenty consecutive patients with CHRP. They used a combination of vitamin E at a dose of 400 IU tid and vitamin C at a dose of 500 mg tid. They assessed the response by symptom index and lifestyle questionnaire. A good number of study patients in the study seem to benefit. This pilot study was not studied further.

Retinol palmitate (vitamin A) has been shown to increase wound healing because of increased collagen cross-linking. This has been used in a randomized study to show improvement of symptoms of chronic radiation proctopathy by Ehrenpreis *et al*[67]. They randomized 19 patients, 10 patients to retinol palmitate group and nine to the placebo group. Five placebo nonresponders were crossed over to the retinol palmitate. The RPSAS scores before and every 30 d for 90 d were measured. The definition of response was a reduction in two or more symptoms or by at least two RPSAS[67]. There was a significant improvement in symptoms in the treatment group compared with the control and also when the controls were crossed over to treatment. But the study was underpowered.

Surgical interventions

Surgery is the last resort in patients with CHRP. Around 10%-25% of patients with CHRP finally need surgery[68]. Intractable bleeding, perforation, stricture, and fistula are some of the indication for surgery in patients with chronic radiation proctitis. There are case reports of non-surgical dilatation for strictures for this condition[69]. Significant improvement of bleeding by diversion has been shown by one of the retrospective study[70]. Fistula with the adjacent structures may need resection or resection with reconstruction with a diverting stoma. Whenever surgical treatment became a necessity, studies report poor outcomes with high complications (15%-80%) and mortality (3%-9%)[70-73]. Since nonoperative interventions are commonly used nowadays in managing patients with CHRP, There are no recently published series on surgical interventions on this issue.

Discussion

Evidence-based medicine requires the systematic and critical evaluation of published and unpublished trials[74]. In 2002, when Denton *et al*[7] first published their systemic review of the non-surgical intervention of late radiation proctitis, they could identify only six randomized controlled trials. The majority of the evidence available was either one individual's or one center's experience with a specific intervention without comparison to a control or another agent. This is probably due to the low incidence of chronic radiation proctitis in the majority of centers and the difficulties that co-exist in compiling a series large enough to be randomized between therapies[34].

Thirteen years later we could identify a total of 14 randomized controlled trials treating 804 patients with CHRP. In many of these studies, we could get the details of the reason for radiation therapy and the dosage. The diagnosis was based on the history and the endoscopic findings. At present, there is no validated score for CHRP, which can be used universally for grading the severity. There can be the inter-observer difference of the same findings. Tissue biopsy may not be conclusive. Patients may not tell their exact symptoms unless directed questions are asked. The severity of the radiation proctitis was graded in many of the studies objectively using symptoms score like RPSAS[1,67] or LENT-SOMA scale[32,60] and intraluminal findings by the sigmoidoscopic or colonoscopic grade (modified Chi grading[1] or Chutkan and Gilinski scales[52]). But different studies used different severity scores and hence the inter-institutional comparison of data is still difficult. The same is true with the outcome measures. Yeoh *et al*[32] have tried to see the rectal functions as well as morphology by using anorectal manometry and endorectal ultrasound. Zhou *et al*[54] have shown the most efficient objective assessment of the response to treatment by using EOCT. There were only a few studies that surveyed the quality of life following treatment[36,60]. However, unlike the previous studies, follow-up of recent studies is fairly long and is usually more than 9 to 12 mo[1,33,36,52,60]. With these randomized trials it is possible to say that there is evidence to make the following judgments: (1) Sucralfate enema appears to have a better effect than anti-inflammatory agents; (2) Anti-inflammatory drugs appear to have a better effect if used with oral metronidazole; (3) Rectal hydrocortisone appears to have a better effect than rectal betamethasone; (4) Sucralfate-steroid retention enema and short chain fatty acid enema are both equally but moderately effective in treating CHRP, but sucralfate-steroid enema is easy to prepare; (5) Four percent formalin is more effective than sucralfate-steroid retention enema and can be effective in 99% of the patients of CHRP; (6) Four percent formalin should be preferred over 10% formalin in treating patients with CHRP since 10% formalin is likely to cause adverse events; (7) Heater probe and bipolar

cautery are equally effective in treating patients with CHRP; (8) Both APC and formalin don't improve the rectal dysfunction but only stop the bleeding; (9) Both APC and formalin are equally effective, but formalin may be better in severe disease; (10) Additional oral treatment after APC will not improve the outcomes; (11) Radiofrequency ablation is a promising upcoming modality of treating CHRP but more robust data in the form of randomized trials needed; (12) HBOT is the only treatment modality, currently, which addresses the underlying problem and effective in treating CHRP patients but is costly and available in a few centers; (13) Vitamin A and other modalities have to be kept in mind while treating these patients since some report shows its efficacy. Further trials and robust data needed to show its efficacy; and (14) Surgical intervention is to be kept as a last resort in patients not responding to any of the methods described above.

Looking at the available evidence, it is clear that there is some improvement in the methodology of these studies. There is an objective assessment of symptoms and signs and also the objective assessment of the outcomes in some of these studies. The major drawback is that the objective assessment is not uniform, different studies using different scores. Also, not much importance is given to the quality of life assessment following treatment. It has been felt by the previous reviewers that one study, even if well conducted, will not be able to modify the changes in practice[7]. It has been felt by Denton *et al*[7] that in order to increase recruitment to trials a national registry of CHRP cases would facilitate multicenter trials with uniform entry criteria, uniform baseline and uniform therapeutic assessments providing standardized outcome data[75].

Limitations of this review: The search was limited to PubMed/Medline, Google and Google Scholar and was not complete and was limited to English language journals only. Individual authors were not contacted.

CONCLUSION

Based on this evidence, it can be concluded that the first line treatment of a patient with CHRP, the most effective way of treating CHRP, should be 4% formalin application. Since it is cheap, easily available, can be applied easily and effective in 99% of the patients. If the radiation proctitis extends beyond rectum, then APC will be a better alternative. Alternatively, both formalin and APC can be used as complementary methods. Those patients who are refractory to formalin or APC may be referred for treatment with HBOT. In centers where radiofrequency ablation is available, further randomized studies should be done to see the efficacy of it in treating patients with CHRP. Those patients with CHRP who do not respond to any of the modality may need surgery in the form of diversion colostomy. Those patients with CHRP presenting with complications like stricture, fistula or other complications like obstructions may need surgery at presentation.

REFERENCES

1 **Nelamangala Ramakrishnaiah VP**, Javali TD, Dharanipragada K, Reddy KS, Krishnamachari S. Formalin dab, the effective way of treating haemorrhagic radiation proctitis: a randomized trial from a tertiary care hospital in South India. *Colorectal Dis* 2012; **14**: 876-882 [PMID: 22356304 DOI: 10.1111/j.1463-1318.2012.03008.x]

2 **Do NL**, Nagle D, Poylin VY. Radiation proctitis: current strategies in management. *Gastroenterol Res Pract* 2011; **2011**: 917941 [PMID: 22144997 DOI: 10.1155/2011/917941]

3 **Agrawal PP**, Bansal N, Bahadur AK, Singh K, Rathi AK. Management of chronic hemorrhagic radiation proctitis. *Asia-Pac J Clin Onco* 2007; **3**: 19-29 [DOI: 10.1111/j.1743-7563.2006.00084.x]

4 **Peppercorn MA**. Sulfasalazine. Pharmacology, clinical use, toxicity, and related new drug development. *Ann Intern Med* 1984; **101**: 377-386 [PMID: 6147110 DOI: 10.7326/0003-4819-101-3-377]

5 **Nagashima R**. Mechanisms of action of sucralfate. *J Clin Gastroenterol* 1981; **3**: 117-127 [PMID: 6798100]

6 **Kochhar R**, Patel F, Dhar A, Sharma SC, Ayyagari S, Aggarwal R, Goenka MK, Gupta BD, Mehta SK. Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. *Dig Dis Sci* 1991; **36**: 103-107 [PMID: 1670631 DOI: 10.1007/BF01300096]

7 **Denton AS**, Andreyev HJ, Forbes A, Maher EJ. Systematic review for non-surgical interventions for the management of late radiation proctitis. *Br J Cancer* 2002; **87**: 134-143 [PMID: 12107832 DOI: 10.1038/sj.bjc.6600360]

8 **Rougier P**, Zimmerman P, Pignon JP, Kac J, Crespon B, Zrihen E, Charbit MF. Rectitesradiques: Efficatecomparee de deux types de corticoids adminstrelocalement. *Med Chir Dig* 1992; **21**: 91-93 (cited - 7) [DOI: 10.1038/sj.bjc.6600360]

9 **Cavcić J**, Turcić J, Martinac P, Jelincić Z, Zupancić B, Panijan-Pezerović R, Unusić J. Metronidazole in the treatment of chronic radiation proctitis: clinical trial. *Croat Med J* 2000; **41**: 314-318 (cited - 7) [PMID: 10962052]

10 **Grigsby PW**, Pilepich MV, Parsons CL. Preliminary results of a phase I/II study of sodium pentosanpolysulfate in the treatment of chronic radiation-induced proctitis. *Am J Clin Oncol* 1990; **13**: 28-31 [PMID: 1689537 DOI: 10.1097/00000421-199002000-00008]

11 **Aalkjaer C**. Short chained fatty acids and the colon: how do they cause vasodilatation? *J Physiol* 2002; **538**: 674 [PMID: 11826156 DOI: 10.1113/jphysiol.2001.015115]

12 **Talley NA**, Chen F, King D, Jones M, Talley NJ. Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled, cross-over pilot trial. *Dis Colon Rectum* 1997; **40**: 1046-1050 [PMID: 9293933 DOI: 10.1007/BF02050927]

13 **Pinto A**, Fidalgo P, Cravo M, Midões J, Chaves P, Rosa J, dos Anjos Brito M, Leitão CN. Short chain fatty acids are effective in short-term treatment of chronic radiation proctitis: randomized, double-blind, controlled trial. *Dis Colon Rectum* 1999; **42**: 788-795; discussion 795-796 [PMID: 10378604 DOI: 10.1007/BF02236937]

14 **Senthil Kumar R**, Vivekanandan S, Pai D, Sahai A, Narasimhan R. Prospective randomised double blind controlled trial to compare rectal sucralfate-steroid combination enema and short chain fatty acid enema in patients with radiation induced proctosigmoiditis. A dissertation submitted to Pondicherry University in partial fulfillment of the requirement for the award of the degree of M.S. Surgery. 2001

15 **Rubinstein E**, Ibsen T, Rasmussen RB, Reimer E, Sørensen BL. Formalin treatment of radiation-induced hemorrhagic proctitis. *Am J Gastroenterol* 1986; **81**: 44-45 [PMID: 3484606]

16 **Seow-Choen F**, Goh HS, Eu KW, Ho YH, Tay SK. A simple and effective treatment for hemorrhagic radiation proctitis using formalin. *Dis Colon Rectum* 1993; **36**: 135-138 [PMID: 8425416 DOI: 10.1007/BF02051168]

17 **Mathai V**, Seow-Choen F. Endoluminal formalin therapy for haemorrhagic radiation proctitis. *Br J Surg* 1995; **82**: 190 [PMID: 7749685 DOI: 10.1002/bjs.1800820216]

18 **Biswal BM**, Lal P, Rath GK, Shukla NK, Mohanti BK, Deo S. Intrarectal formalin application, an effective treatment for grade III

haemorrhagic radiation proctitis. *Radiother Oncol* 1995; **35**: 212-215 [PMID: 7480824 DOI: 10.1016/0167-8140(95)01565-X]
19 **Saclarides TJ**, King DG, Franklin JL, Doolas A. Formalin instillation for refractory radiation-induced hemorrhagic proctitis. Report of 16 patients. *Dis Colon Rectum* 1996; **39**: 196-199 [PMID: 8620787 DOI: 10.1007/BF02068075]
20 **Roche B**, Chautems R, Marti MC. Application of formaldehyde for treatment of hemorrhagic radiation-induced proctitis. *World J Surg* 1996; **20**: 1092-1094; discussion 1094-1095 [PMID: 8798370 DOI: 10.1007/s002689900166]
21 **Chapuis P**, Dent O, Bokey E, Galt E, Zelas P, Nicholls M, Yuile P, Mameghan H. The development of a treatment protocol for patients with chronic radiation-induced rectal bleeding. *Aust N Z J Surg* 1996; **66**: 680-685 [PMID: 8855923 DOI: 10.1111/j.1445-2197.1996.tb00717.x]
22 **Yegappan M**, Ho YH, Nyam D, Leong A, Eu KW, Seow C. The surgical management of colorectal complications from irradiation for carcinoma of the cervix. *Ann Acad Med Singapore* 1998; **27**: 627-630 [PMID: 9919329]
23 **Counter SF**, Froese DP, Hart MJ. Prospective evaluation of formalin therapy for radiation proctitis. *Am J Surg* 1999; **177**: 396-398 [PMID: 10365878 DOI: 10.1016/S0002-9610(99)00072-0]
24 **Pikarsky AJ**, Belin B, Efron J, Weiss EG, Nogueras JJ, Wexner SD. Complications following formalin installation in the treatment of radiation induced proctitis. *Int J Colorectal Dis* 2000; **15**: 96-99 [PMID: 10855551 DOI: 10.1007/s003840050240]
25 **Ismail MA**, Qureshi MA. Formalin dab for haemorrhagic radiation proctitis. *Ann R Coll Surg Engl* 2002; **84**: 263-264 [PMID: 12215030]
26 **Luna-Pérez P**, Rodríguez-Ramírez SE. Formalin instillation for refractory radiation-induced hemorrhagic proctitis. *J Surg Oncol* 2002; **80**: 41-44 [PMID: 11967906 DOI: 10.1002/jso.10095]
27 **Ouwendijk R**, Tetteroo GW, Bode W, de Graaf EJ. Local formalin instillation: an effective treatment for uncontrolled radiation-induced hemorrhagic proctitis. *Dig Surg* 2002; **19**: 52-55 [PMID: 11961356 DOI: 10.1159/000052006]
28 **Chautems RC**, Delgadillo X, Rubbia-Brandt L, Deleaval JP, Marti MC, Roche B. Formaldehyde application for haemorrhagic radiation-induced proctitis: a clinical and histological study. *Colorectal Dis* 2003; **5**: 24-28 [PMID: 12780922 DOI: 10.1046/j.1463-1318.2003.00396.x]
29 **Parikh S**, Hughes C, Salvati EP, Eisenstat T, Oliver G, Chinn B, Notaro J. Treatment of hemorrhagic radiation proctitis with 4 percent formalin. *Dis Colon Rectum* 2003; **46**: 596-600 [PMID: 12792434 DOI: 10.1007/s10350-004-6614-1]
30 **de Parades V**, Etienney I, Bauer P, Bourguignon J, Meary N, Mory B, Sultan S, Taouk M, Thomas C, Atienza P. Formalin application in the treatment of chronic radiation-induced hemorrhagic proctitis--an effective but not risk-free procedure: a prospective study of 33 patients. *Dis Colon Rectum* 2005; **48**: 1535-1541 [PMID: 15933799 DOI: 10.1007/s10350-005-0030-z]
31 **Haas EM**, Bailey HR, Farragher I. Application of 10 percent formalin for the treatment of radiation-induced hemorrhagic proctitis. *Dis Colon Rectum* 2007; **50**: 213-217 [PMID: 17080283 DOI: 10.1007/s10350-006-0707-y]
32 **Yeoh E**, Tam W, Schoeman M, Moore J, Thomas M, Botten R, Di Matteo A. Argon plasma coagulation therapy versus topical formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2013; **87**: 954-959 [PMID: 24113059 DOI: 10.1016/j.ijrobp.2013.08.034]
33 **Guo GH**, Yu FY, Wang XJ, Lu F. A randomized controlled clinical trial of formalin for treatment of chronic hemorrhagic radiation proctopathy in cervical carcinoma patients. *Support Care Cancer* 2015; **23**: 441-446 [PMID: 25128068 DOI: 10.1007/s00520-014-2401-2]
34 **Wong MT**, Lim JF, Ho KS, Ooi BS, Tang CL, Eu KW. Radiation proctitis: a decade's experience. *Singapore Med J* 2010; **51**: 315-319 [PMID: 20505910]
35 **Alfadhli AA**, Alazmi WM, Ponich T, Howard JM, Prokopiw I, Alaqeel A, Gregor JC. Efficacy of argon plasma coagulation compared to topical formalin application for chronic radiation proctopathy. *Can J Gastroenterol* 2008; **22**: 129-132 [PMID: 18299729 DOI: 10.1155/2008/964912]
36 **Sahakitrungruang C**, Patiwongpaisarn A, Kanjanasilp P, Malakorn S, Atittharnsakul P. A randomized controlled trial comparing colonic irrigation and oral antibiotics administration versus 4% formalin application for treatment of hemorrhagic radiation proctitis. *Dis Colon Rectum* 2012; **55**: 1053-1058 [PMID: 22965404 DOI: 10.1097/DCR.0b013e318265720a]
37 **Rustagi T**, Mashimo H. Endoscopic management of chronic radiation proctitis. *World J Gastroenterol* 2011; **17**: 4554-4562 [PMID: 22147960 DOI: 10.3748/wjg.v17.i41.4554]
38 **Johnston MJ**, Robertson GM, Frizelle FA. Management of late complications of pelvic radiation in the rectum and anus: a review. *Dis Colon Rectum* 2003; **46**: 247-259 [PMID: 12576899 DOI: 10.1007/s10350-004-6530-4]
39 **Jensen DM**, Machicado GA, Cheng S, Jensen ME, Jutabha R. A randomized prospective study of endoscopic bipolar electrocoagulation and heater probe treatment of chronic rectal bleeding from radiation telangiectasia. *Gastrointest Endosc* 1997; **45**: 20-25 [PMID: 9013165 DOI: 10.1016/S0016-5107(97)70298-0]
40 **Taylor JG**, Disario JA, Bjorkman DJ. KTP laser therapy for bleeding from chronic radiation proctopathy. *Gastrointest Endosc* 2000; **52**: 353-357 [PMID: 10968849 DOI: 10.1067/mge.2000.107726]
41 **Taylor JG**, DiSario JA, Buchi KN. Argon laser therapy for hemorrhagic radiation proctitis: long-term results. *Gastrointest Endosc* 1993; **39**: 641-644 [PMID: 8224685 DOI: 10.1016/S0016-5107(93)70215-1]
42 **Karamanolis G**, Psatha P, Triantafyllou K. Endoscopic treatments for chronic radiation proctitis. *World J Gastrointest Endosc* 2013; **5**: 308-312 [PMID: 23858374 DOI: 10.4253/wjge.v5.i7.308]
43 **Sebastian S**, O'Connor H, O'Morain C, Buckley M. Argon plasma coagulation as first-line treatment for chronic radiation proctopathy. *J Gastroenterol Hepatol* 2004; **19**: 1169-1173 [PMID: 15377295 DOI: 10.1111/j.1440-1746.2004.03448.x]
44 **Silva RA**, Correia AJ, Dias LM, Viana HL, Viana RL. Argon plasma coagulation therapy for hemorrhagic radiation proctosigmoiditis. *Gastrointest Endosc* 1999; **50**: 221-224 [PMID: 10425416 DOI: 10.1016/S0016-5107(99)70228-2]
45 **Dees J**, Meijssen MA, Kuipers EJ. Argon plasma coagulation for radiation proctitis. *Scand J Gastroenterol Suppl* 2006; **(243)**: 175-178 [PMID: 16782638 DOI: 10.1080/00365520600664300]
46 **Villavicencio RT**, Rex DK, Rahmani E. Efficacy and complications of argon plasma coagulation for hematochezia related to radiation proctopathy. *Gastrointest Endosc* 2002; **55**: 70-74 [PMID: 11756918 DOI: 10.1067/mge.2002.119877]
47 **Lam MC**, Parliament M, Wong CK. Argon plasma coagulation for the treatment of hemorrhagic radiation colitis. *Case Rep Gastroenterol* 2012; **6**: 446-451 [PMID: 22933988 DOI: 10.1159/000339462]
48 **Kwan V**, Bourke MJ, Williams SJ, Gillespie PE, Murray MA, Kaffes AJ, Henriquez MS, Chan RO. Argon plasma coagulation in the management of symptomatic gastrointestinal vascular lesions: experience in 100 consecutive patients with long-term follow-up. *Am J Gastroenterol* 2006; **101**: 58-63 [PMID: 16405534 DOI: 10.1111/j.1572-0241.2006.00370.x]
49 **Swan MP**, Moore GT, Sievert W, Devonshire DA. Efficacy and safety of single-session argon plasma coagulation in the management of chronic radiation proctitis. *Gastrointest Endosc* 2010; **72**: 150-154 [PMID: 20493484 DOI: 10.1016/j.gie.2010.01.065]
50 **Rotondano G**, Bianco MA, Marmo R, Piscopo R, Cipolletta L. Long-term outcome of argon plasma coagulation therapy for bleeding caused by chronic radiation proctopathy. *Dig Liver Dis* 2003; **35**: 806-810 [PMID: 14674672 DOI: 10.1016/S1590-8658(03)00454-7]
51 **Taïeb S**, Rolachon A, Cenni JC, Nancey S, Bonvoisin S, Descos L, Fournet J, Gérard JP, Flourié B. Effective use of argon plasma coagulation in the treatment of severe radiation proctitis. *Dis Colon Rectum* 2001; **44**: 1766-1771 [PMID: 11742159 DOI: 10.1007/BF02234452]

52 **Chruscielewska-Kiliszek MR**, Regula J, Polkowski M, Rupinski M, Kraszewska E, Pachlewski J, Czaczkowska-Kurek E, Butruk E. Sucralfate or placebo following argon plasma coagulation for chronic radiation proctitis: a randomized double blind trial. *Colorectal Dis* 2013; **15**: e48-e55 [PMID: 23006660 DOI: 10.1111/codi.12035]

53 **Nikfarjam M**, Faulx A, Laughinghouse M, Marks JM. Feasibility of radiofrequency ablation for the treatment of chronic radiation proctitis. *Surg Innov* 2010; **17**: 92-94 [PMID: 20504783 DOI: 10.1177/1553350610365701]

54 **Zhou C**, Adler DC, Becker L, Chen Y, Tsai TH, Figueiredo M, Schmitt JM, Fujimoto JG, Mashimo H. Effective treatment of chronic radiation proctitis using radiofrequency ablation. *Therap Adv Gastroenterol* 2009; **2**: 149-156 [PMID: 20593010 DOI: 10.1177/1756283X08103341]

55 **Eddi R**, Depasquale JR. Radiofrequency ablation for the treatment of radiation proctitis: a case report and review of literature. *Therap Adv Gastroenterol* 2013; **6**: 69-76 [PMID: 23320051 DOI: 10.1177/1756283x12456895]

56 **Dray X**, Battaglia G, Wengrower D, Gonzalez P, Carlino A, Camus M, Adar T, Pérez-Roldán F, Marteau P, Repici A. Radiofrequency ablation for the treatment of radiation proctitis. *Endoscopy* 2014; **46**: 970-976 [PMID: 25290097 DOI: 10.1055/s.0034.1377756]

57 **Ritch CR**, Katz AE. Update on cryotherapy for localized prostate cancer. *Curr Urol Rep* 2009; **10**: 206-211 [PMID: 19371478 DOI: 10.1007/s11934-009-0035-6]

58 **Hou JK**, Abudayyeh S, Shaib Y. Treatment of chronic radiation proctitis with cryoablation. *Gastrointest Endosc* 2011; **73**: 383-389 [PMID: 21295650 DOI: 10.1016/j.gie.2010.10.044]

59 **Moawad FJ**, Maydonovitch CL, Horwhat JD. Efficacy of cryospray ablation for the treatment of chronic radiation proctitis in a pilot study. *Dig Endosc* 2013; **25**: 174-179 [PMID: 23362977 DOI: 10.1111/j.1443-1661.2012.01355.x]

60 **Clarke RE**, Tenorio LM, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, Desai SP, Dominguez Parra L, Rodrigues SD, Long RJ, Walker MB. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; **72**: 134-143 [PMID: 18342453 DOI: 10.1016/j.ijrobp.2007.12.048]

61 **Tahir AR**, Westhuyzen J, Dass J, Collins MK, Webb R, Hewitt S, Fon P, McKay M. Hyperbaric oxygen therapy for chronic radiation-induced tissue injuries: Australasia's largest study. *Asia Pac J Clin Oncol* 2015; **11**: 68-77 [PMID: 25382755 DOI: 10.1111/ajco.12289]

62 **Warren DC**, Feehan P, Slade JB, Cianci PE. Chronic radiation proctitis treated with hyperbaric oxygen. *Undersea Hyperb Med* 1997; **24**: 181-184 [PMID: 9308141]

63 **Girnius S**, Cersonsky N, Gesell L, Cico S, Barrett W. Treatment of refractory radiation-induced hemorrhagic proctitis with hyperbaric oxygen therapy. *Am J Clin Oncol* 2006; **29**: 588-592 [PMID: 17148996 DOI: 10.1097/01.coc.0000236004.95384.5b]

64 **Jones K**, Evans AW, Bristow RG, Levin W. Treatment of radiation proctitis with hyperbaric oxygen. *Radiother Oncol* 2006; **78**: 91-94 [PMID: 16337705 DOI: 10.1016/j.radonc.2005.11.004]

65 **Dall'Era MA**, Hampson NB, Hsi RA, Madsen B, Corman JM. Hyperbaric oxygen therapy for radiation induced proctopathy in men treated for prostate cancer. *J Urol* 2006; **176**: 87-90 [PMID: 16753375 DOI: 10.1016/S0022-5347(06)00491-5]

66 **Kennedy M**, Bruninga K, Mutlu EA, Losurdo J, Choudhary S, Keshavarzian A. Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. *Am J Gastroenterol* 2001; **96**: 1080-1084 [PMID: 11316150]

67 **Ehrenpreis ED**, Jani A, Levitsky J, Ahn J, Hong J. A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy. *Dis Colon Rectum* 2005; **48**: 1-8 [PMID: 15690650 DOI: 10.1007/s10350-004-0821-7]

68 **Jao SW**, Beart RW, Gunderson LL. Surgical treatment of radiation injuries of the colon and rectum. *Am J Surg* 1986; **151**: 272-277 [PMID: 3946764 DOI: 10.1016/0002-9610(86)90086-3]

69 **Johansson C**. Endoscopic dilation of rectal strictures: a prospective study of 18 cases. *Dis Colon Rectum* 1996; **39**: 423-428 [PMID: 8878503 DOI: 10.1007/BF02054058]

70 **Ayerdi J**, Moinuddeen K, Loving A, Wiseman J, Deshmukh N. Diverting loop colostomy for the treatment of refractory gastrointestinal bleeding secondary to radiation proctitis. *Mil Med* 2001; **166**: 1091-1093 [PMID: 11778411]

71 **Pricolo VE**, Shellito PC. Surgery for radiation injury to the large intestine. Variables influencing outcome. *Dis Colon Rectum* 1994; **37**: 675-684 [PMID: 8026234 DOI: 10.1007/BF02054411]

72 **Anseline PF**, Lavery IC, Fazio VW, Jagelman DG, Weakley FL. Radiation injury of the rectum: evaluation of surgical treatment. *Ann Surg* 1981; **194**: 716-724 [PMID: 7305485 DOI: 10.1097/00000658-198112000-00010]

73 **Lucarotti ME**, Mountford RA, Bartolo DC. Surgical management of intestinal radiation injury. *Dis Colon Rectum* 1991; **34**: 865-869 [PMID: 1914719 DOI: 10.1007/BF02049698]

74 **Denton AS**, Bentzen SM, Maher EJ. How useful are observational reports in the evaluation of interventions for radiation morbidity?: an analysis of formalin therapy for late radiation proctitis. *Radiother Oncol* 2002; **64**: 291-295 [PMID: 12242117 DOI: 10.1016/S0167-8140(02)00138-X]

75 **Henson C**. Chronic radiation proctitis: issues surrounding delayed bowel dysfunction post-pelvic radiotherapy and an update on medical treatment. *Therap Adv Gastroenterol* 2010; **3**: 359-365 [PMID: 21180615 DOI: 10.1177/1756283x10371558]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Early surgery in Crohn's disease a benefit in selected cases

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Abstract

AIM: To compare the outcomes of a cohort of Crohn's disease (CD) patients undergoing early surgery (ES) to those undergoing initial medical therapy (IMT).

METHODS: We performed a review of a prospective database CD patients managed at a single tertiary institution. Inclusion criteria were all patients with ileal or ileocolonic CD between 1995-2014. Patients with incomplete data, isolated colonic or perianal CD were excluded. Primary endpoints included the need for, and time to subsequent surgery. Secondary endpoints included the number and duration of hospital admissions, and medical therapy.

RESULTS: Forty-two patients underwent ES and 115 underwent IMT. The operative intervention rate at 5 years in the ES group was 14.2% *vs* IMT 31.3% (HR = 0.41, 95%CI: 0.23-0.72, P = 0.041). The ES group had fewer hospital admissions per patient [median 1 *vs* 3 (P = 0.012)] and fewer patients required anti-TNF therapy than IMT (33.3% *vs* 57%, P = 0.003). A subgroup analysis of 62 IMT patients who had undergone surgery were compared to ES patients, and showed similar 5 year (from index surgery) re-operation rates 16.1% *vs* 14.3%. In this subset, a significant difference was still found in median number of hospital admissions favouring ES, 1 *vs* 2 (P = 0.002).

CONCLUSION: Our data supports other recent studies suggesting that patients with ileocolonic CD may have a more benign disease course if undergoing early surgical intervention, with fewer admissions to hospital and a

trend to reduced overall operation rates.

Key words: Crohn's disease; Surgery; Inflammatory bowel disease; Terminal ileitis; Operation

Core tip: This study supports the growing body of evidence that asserts that selected patients with ileocolonic Crohn's have reduced requirement for medical therapy and a trend to fewer surgical interventions. Expanding on the evidence, this study also demonstrated fewer admissions to hospital for Crohn's disease related illness.

An V, Cohen L, Lawrence M, Thomas M, Andrews J, Moore J. Early surgery in Crohn's disease a benefit in selected cases. *World J Gastrointest Surg* 2016; 8(7): 492-500 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i7/492.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i7.492

INTRODUCTION

Surgery is often an integral part of the management algorithm for patients with Crohn's disease (CD), with up to 20%-40% requiring surgery within in their first year[1-4] and up to 80% at some time during their disease[5]. As a chronic condition with a relapsing remitting course, surgery does not provide cure, but is an adjunct for the management of acute complications of penetrating and stricturing disease and also after maximal medical therapy fails to control disease or presents unacceptable side effects. Advances in medical therapy have seen a reduction in long-term steroid use and longer disease remission. Despite these advances older studies suggest no reduction in the proportion of patients requiring surgery. In a retrospective series, Cosnes *et al*[6], reported that 35% patients required surgery at 5 years, which was the same as historical cohorts.

However, the advent of biologic agents has significantly influenced the clinical course of patients of CD and also surgical decision-making. ACCENT 1 reported higher clinical remission (OR = 2.7) in patients receiving maintenance infliximab compared with placebo[7]. Similar findings have been reported for Adalimumab with higher rates of clinical remission compared with placebo (36% *vs* 12%)[8]. Additionally in a report from the Nationwide Inpatient Sample in the United States, rates of surgical intervention have fallen from 17.3% in 1997 to 12.4% in 2007[9].

Contention exists in the literature regarding the optimal timing of surgery in the management algorithm of CD, particularly in patients with short segment disease where resection of all macroscopic disease is feasible. Some evidence suggests that early surgery (ES) in CD may lead to a longer time to clinical recurrence[10] and lower long-term reoperation rate (14% at 5 years) compared with later surgery (30% at 5 years)[11]. Additionally, ES cohorts are reported to have reduced requirements for steroids and immunosuppression[3,11]. This study aims to determine whether patients who have ES for ileal or ileocolonic CD run a more benign clinical course, as determined by the need for fewer operations, hospital admissions and the ongoing medical therapy required for disease control than those managed with conventional medical therapy.

MATERIALS AND METHODS

This study is a cohort comparison study between patients who underwent ES compared with those that underwent initial medical therapy (IMT). We examined a consecutive series of patients with ileal and ileocolonic CD managed at a major metropolitan teaching hospital from 1995 to 2014. Data were extracted from a clinical IBD database within the IBD service at the Royal Adelaide Hospital. This database was prospectively maintained from 2007, and prior to this, data were sourced from case notes review. Additional data were collected from review of medical records and pathology records.

ES was defined as patients who have undergone upfront surgery for CD due to an acute complication and those who underwent surgery within 6 mo of their diagnosis of CD. This arbitrary time frame was chosen as within this time period there is limited scope to have established of medical therapy. Acute complications included abdominal pain with peritonism, obstruction, perforation or fistulisation. The IMT cohort included patients with a histological or clinical diagnosis of CD made after 1995 referred to our health service who have undergone at least 6 mo of medical therapy. Patients diagnosed prior to this date were excluded. Patients in this cohort who went on to require bowel resection for their disease were also identified for a subgroup analysis and considered to have deferred surgery (DS).

Data collected included patient demographics, disease phenotype according to the Montreal classification[12], medical and surgical therapy. The primary endpoint for each patient was need for subsequent surgical resection. Secondary endpoints were the number of hospitalizations and days in hospital over the duration of their disease. All inpatient care data (number of admissions and total length of stay) were captured by a statewide computer database, which records admissions to all public hospitals within the state in this period.

Inclusion criteria were patients with ileal or ileocolonic CD, with or without perianal involvement. Patients with isolated colonic or isolated perianal CD or those with incomplete records were excluded.

Data regarding patients' medical therapy for CD were collected, but due to the retrospective nature of

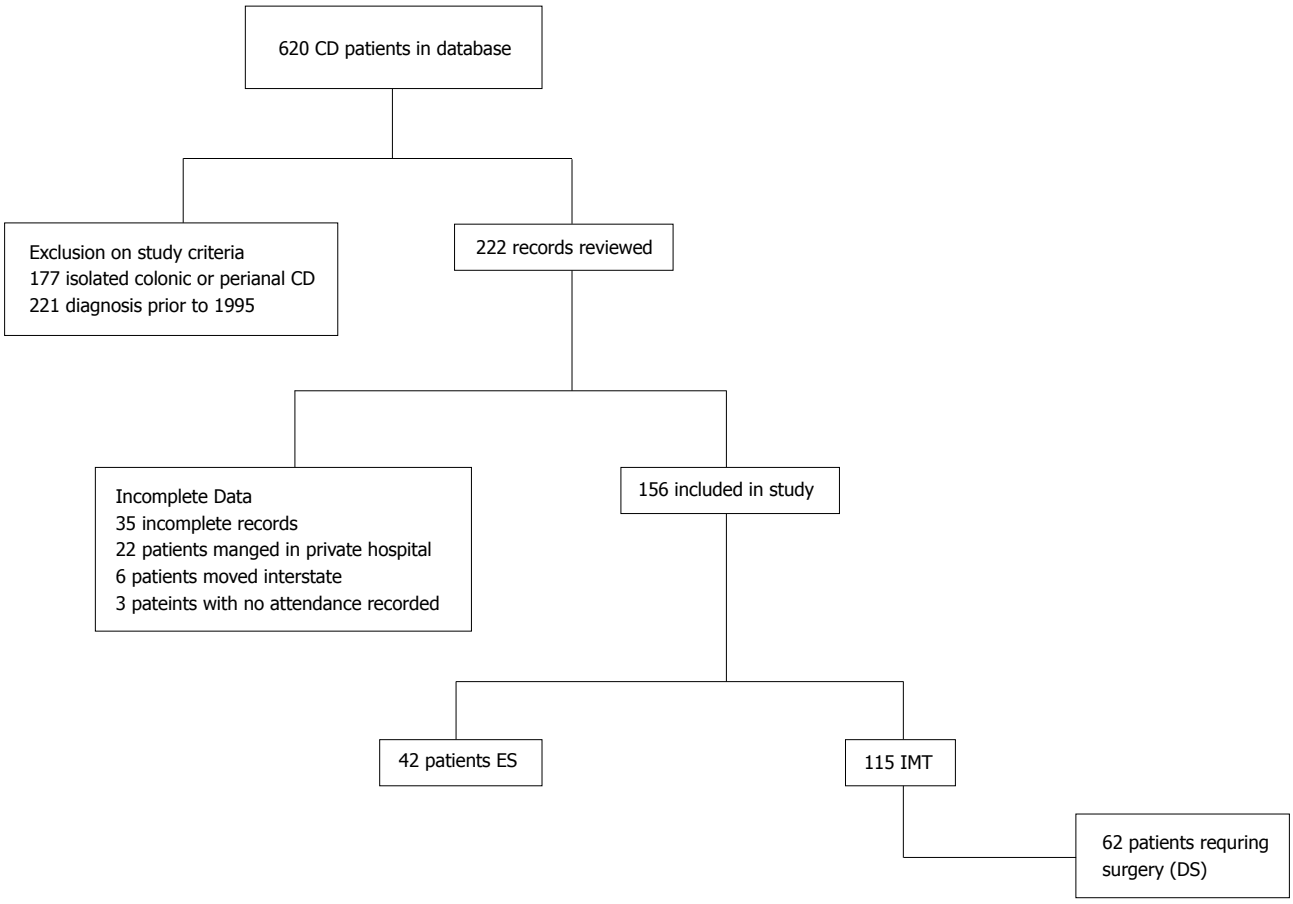

Figure 1 Consort diagram. ES: Early surgery; IMT: Initial medical therapy; DS: Deferred surgery; CD: Crohn's disease.

the database prior to 2007, the accuracy of fine details such as time course, dose and duration of therapy could not be assured. Consequently, medical therapies received by each patient are reported as a categorical outcome, described by type of treatment (none, steroid, immunosuppressive or biologic therapy).

This project was reviewed and approved by the Royal Adelaide Hospital Human Research Ethics committee. As this was a clinical audit, individual patient consent was not necessary and not sought. Data were tabulated in a Microsoft Excel™ spreadsheet. Statistical analyses were performed utilizing SPSS™ ver. 22. Differences between groups were compared using the χ^2 test for categorical data, and ordinal data were compared using the Student's *t*-test or Mann-Whitney-*U* test for non-parametric distributions. To determine a difference in time to further surgery between groups, Kaplan-Meier analyses were performed and differences tested using the Mantel-Cox log rank test.

RESULTS

A total of 620 patients with CD were identified on the database. Exclusions are shown on a consort diagram (Figure 1). A total of 157 patients met inclusion criteria and were included in the study. There were 42 patients in the ES cohort, who either presented with an acute complication requiring emergency surgery or underwent an operation within 6 m of diagnosis due to a progression or complication of CD. The remaining 115 patients were treated with IMT, 62 (53.9%) of whom underwent surgery by the end of the study period (DS).

Demographics of the cohorts are shown in Table 1. Patients in the ES group were significantly older with a median age at diagnosis of 34.5 years (24-45) compared to 24 (19-33) in the IMT group ($P = 0.0001$) and a shorter duration of disease (ES 5.6 years, IMT 8.9, $P = 0.014$). Not surprisingly, ES patients were more likely to have a stricturing or penetrating phenotype than IMT patients. The DS cohort, who were medically treated patients who went on to have a resection, had the same proportion of patients with penetrating and stricturing disease (B2 and B3), 38.7% and 54.8% respectively as the ES patients (40.5% and 52.4% respectively $P = 0.968$). There was also a significant difference in disease location, with a higher proportion of L3 disease compared to L1 disease and subsequently in the proportion of patients with perianal disease in the IMT cohort.

Table 2 outlines the mode of presentation of patients requiring ES. Over half the ES cohort presented with either acute obstruction or perforation necessitating emergency surgery and data was unavailable for 5 patients in this cohort. In contrast, of the patients in

Table 1 Demographic and clinical data *n* (%)

Clinical details	Early surgery (*n* = 42)	Initial medical therapy (*n* = 115)			
		IMT (*n* = 115)	*P* value	DS (*n* = 62)[1]	*P* value
Gender M:F	22:20	50:65	0.531	24:38:00	0.227
Age at diagnosis (yr), median (IQR)	34.5 (24-46)	24 (19-33)	0.0001	23.5 (18.25-31.75)	0.006
Smoking	15 (35.7)	43 (37.4)	0.852	25 (40.3)	0.685
Phenotype					
B1 (non-stricturing)	3 (7.1)	38 (36.2)	0.001	4 (6.5)	0.968
B2 (stricturing)	17 (40.5)	26 (24.8)		24 (38.7)	
B3 (penetrating)	22 (52.4)	41 (39.0)		34 (54.8)	
Location					
L1 (ileal)	28 (66.7)	25 (24.5)	0.0001	17 (26.3)	0.0001
Perianal disease	0	6 (5.2)		3 (4.8)	
L3 (ileocolonic)					
Perianal disease	14 (33.3)	74 (69.4)		45 (70.2)	
	5 (11.9)	40 (34.8)		16 (25.8)	

[1]Patients in the DS group are a subset of IMT patients. IMT: Initial medical therapy; DS: Deferred surgery; IQR: Interquartile range; M: Male; F: Female.

Table 2 Indications for early surgery *n* (%)

Clinical details	Early surgery (*n* = 42)	Deferred surgery (*n* = 62)
Indication for surgery		
Acute obstruction – emergency resection	9 (21.4)	4 (23.0)
Subacute obstruction – elective resection	-	20 (32.3)
Perforation	15 (35.7)	7 (11.3)
Fistula/phlegmon	5 (11.9)	15 (24.2)
Abdominal pain	5 (11.9)	2 (3.2)
Haemorrhage	3 (7.1)	-
Not specified	5 (11.9)	14 (23.0)

the DS cohort, 11 patients presented with an acute complication necessitating emergency surgery despite upfront medical therapy, 4 with acute obstruction and 7 with perforation. Thirty-five (56.5%) of the DS cohort required surgery due to progression in obstructive symptoms (6.5%) or fistula formation (24.2%).

The number of patients in each cohort requiring surgical resection, hospital admission and medical therapy is shown in Table 3. The proportion of patients requiring subsequent resection at 5 years was significantly lower in the ES group compared with the IMT group (14.2% *vs* 31.3%, $P = 0.041$). Of note though, 57.3% of IMT patients required no surgery. Endpoints for the DS subgroup of patients were determined from the time of their index operation, allowing a fairer comparison to the ES group, as the two cohorts have all undergone one operation. The rate of subsequent surgery in the subgroup of 62 DS patients was 16.1%, which was not significantly different to the ES cohort. The median duration of between diagnosis and index operation in the DS cohort was 46.4 mo (IQR 23-97). The extent of resection and need for stoma were similar in each group and shown in Table 4.

The ES group had a higher estimated proportion of patients not having a subsequent resection at 10 years than those having IMT (Figure 2) (83.7% *vs* 52.7%; $P_{\text{Log-rank}} = 0001$). The comparison of ES to DS groups is shown in Figure 3 with an estimated probability of no subsequent surgery at 10 years of 83.7% and 43.7% ($P_{\text{Log-rank}} = 0.032$) respectively.

The median number of hospital admissions differed between the two groups, with the ES group having fewer admissions than each of the IMT and DS patients (ES 1 *vs* IMT 3, $P = 0.012$) and *vs* (DS subset 2, $P = 0.002$). The median number of days in hospital over the duration of each patients' disease did not differ significantly between the groups. However, this includes the index admission for surgery in the ES cohort.

Rates of immunomodulator and steroid use were similar when comparing the ES group to both IMT and DS cohorts. The proportion of patients receiving biologic therapy was significantly lower in the ES cohort than those having IMT (ES 33.3% *vs* IMT 60.0%, $P = 0.004$) and also the DS subgroup (ES 33.3% *vs* DS 67.7%, $P = 0.001$). The proportion of patients requiring no treatment for their disease differed between the groups (ES 23.8% *vs* IMT 4.3% *vs* DS 0%, $P < 0.0001$).

DISCUSSION

CD remains a challenging chronic condition where there has been a progressive evolution in the positioning and roles of medical and surgical therapy. Our study has found that 31.3% of patients initially managed with medical therapy will come to surgery within 5 years, in line with other studies[2,4,6,13]. This is significantly higher than the 5 year subsequent resection rate of those patients undergoing ES (14.2%).

An alternative interpretation of our data is that 68.7% of patients undergoing medical therapy avoided the need for surgery altogether within a 5 year period. However, the IMT cohort likely represented a less aggressive phenotype of CD as demonstrated by lower rates of stricturing and penetrating disease in this group compared with the ES group. The IMT patients who have had subsequent surgery (DS), had a similar phenotype to the ES group and comparison between

Table 3 Comparison of early *vs* initial medical therapy in Crohn's disease *n* (%)

Clinical details	Early surgery (*n* = 42)	Initial medical therapy (*n* = 115)			
		Initial medical therapy (*n* = 115)	*P* value	Deferred surgery (*n* = 62)[1]	*P* value
Number requiring surgery					
3 yr	5 (11.9)	24 (20.7)	0.250	5 (8.1)	0.521
5 yr	6 (14.2)	36 (31.3)	0.041	10 (16.1)	NS
Completion of study period	7 (16.7)	62 (53.9)	< 0.0001	20 (32.3)	0.110
Number of admission to hospital per patient, median (IQR)	1 (1-2)	3 (1-5)	0.012	2 (1-4.5)	0.002
Days in hospital (d), median (IQR)	12.5 (9-22.5)	11 (3-28)	0.230	17 (8-28)	0.347
Medical therapy					
Immune modulator	32 (76.2)	101 (87.8)	0.083	54 (87.1)	0.189
Steroids	12 (28.6)	34 (29.6)	NS	23 (37.1)	0.404
Anti-TNF	14 (33.3)	69 (60.0)	0.004	42 (67.7)	0.001
No requirement for medical therapy	10 (23.8)	5 (4.3)	0.008	0 (0)	< 0.0001
Follow-up months (mo), median (IQR)	67 (31-114)	97 (58-150)		64 (19-121)	

[1]Data for this subset regarding length of stay and hospital admissions was taken from the date of first operation and not from date of diagnosis. IQR: Interquartile range; TNF: Tumour necrosis factor; NS: Not significant.

Table 4 Comparison of extent of resection performed in early surgery *vs* deferred surgery cohorts *n* (%)

Clinical details	Early surgery (*n* = 42)	Deferred surgery (*n* = 62)	*P* value
Operation			
Small bowel resection	5 (11.9)	7 (11.3)	NS
Ileocolic resection	31 (73.8)	30 (48.4)	0.015
Small bowel and segmental colonic resection	3 (7.1)	9 (14.5)	0.352
Small bowel and total colectomy	2 (4.8)	9 (14.5)	0.193
Data unavailable	1 (2.9)	7 (11.3)	0.139
Stoma formation	3 (7.1)	5 (8.1)	NS

NS: Not significant.

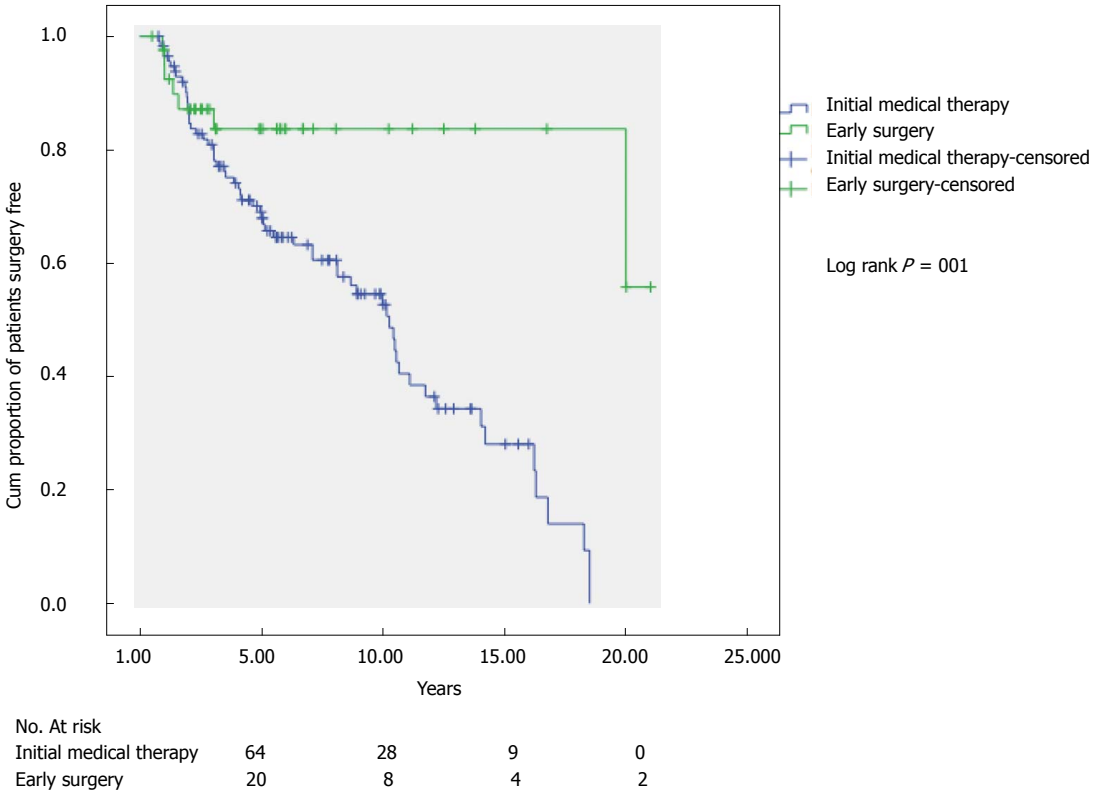

Figure 2 Cumulative event curve time to subsequent surgical resection in early surgery *vs* initial medical therapy.

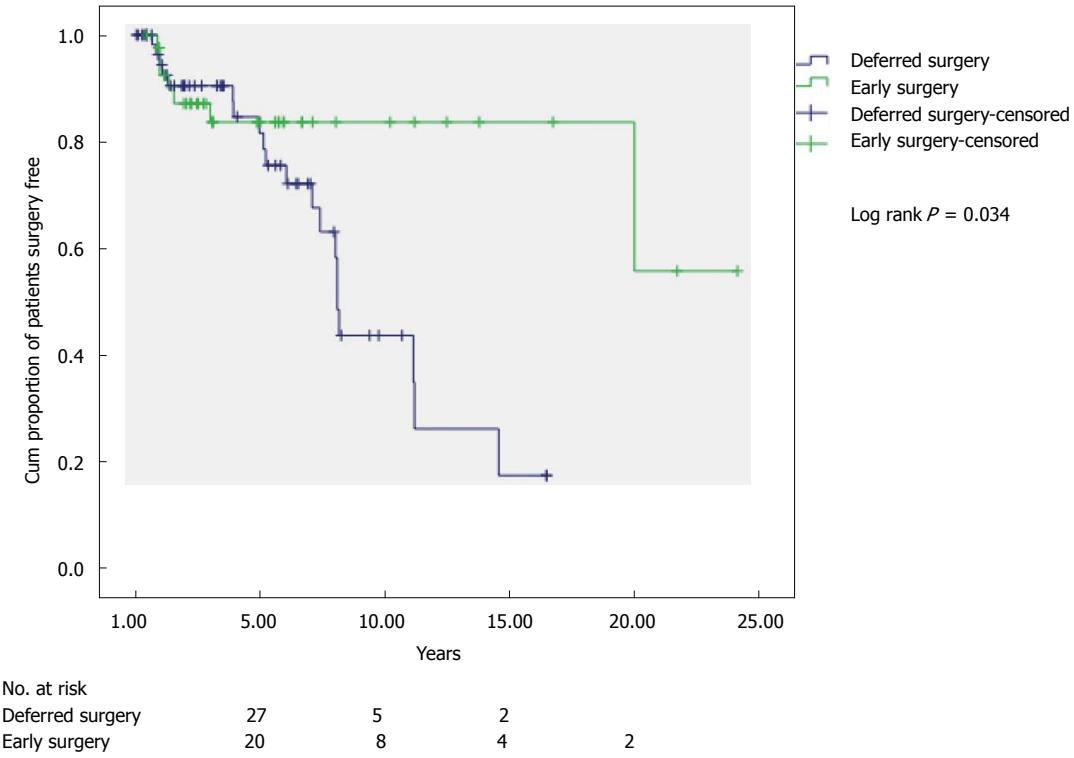

Figure 3 Cumulative event curve: Time to further surgical resection in early surgery *vs* deferred surgery.

these two groups may be more relevant. Indeed at 5 years, similar numbers had had further resection (ES 14.2% *vs* DS 16.1%), even a trend to higher rates of surgery in the DS group by the end of the study (ES 16.7% *vs* DS 32.3%). The estimated proportion of patients not requiring subsequent surgery at 10 years for the ES and DS groups were 83.7% and 43.7% respectively. These findings are similar to reports by Golovics *et al*[3] and Latella *et al*[11], which give validation to these results across different healthcare settings in different countries.

This is the only study to the authors' knowledge that additionally examined inpatient healthcare utilization (hospital admissions and length total cumulative of stay) as an endpoint in comparing ES and IMT. The ES patients had fewer hospital admissions for the duration of their disease than IMT patients and the subset of DS patients [ES 67, IMT 107, DS 50 (median, months)] suggesting disease control may be better in the ES group. However a conservative interpretation of this is necessary given the longer follow-up and higher incidence of L3 and perianal disease in the IMT group.

What is difficult to quantify in the literature is the health related quality of life (HRQOL) of medically managed patients. There is a paucity of data in the literature examining this, whilst more surgical data exist with Thirlby *et al*[14] reporting an improvement in 7 of 8 domains in HRQOL at 12 mo after surgical resection. Casellas *et al*[15] reported significant differences in HRQOL scores between patients with active disease and those in disease remission. Such assessments at different time intervals of the two cohorts would be valuable in determining the true effect of ES and whether early resection conferred an improvement in quality of life and disease control.

We did not find a difference in steroid use between the groups, unlike Aratari *et al*[10]. who reported a need for corticosteroid therapy in 39.8% of ES patients compared with 62.1% of medically treated CD at 5 years. The similar rates of immunomodulator use we observed in ES and IMT patients, 76.2% and 87.8% respectively, are in line with current evidence supporting pro-active tailored post resection therapy to reduce clinical and endoscopic recurrence[16-18].

Immune modulators and biologic agents have added to the armamentarium of medical therapy for CD. Careful consideration should be given regarding the timing of surgery in patients with ileal CD, especially where there is a stricturing or penetrating phenotype, and this should be balanced against the aggressive pursuit of medically induced clinical remission. This balance of medical therapy and surgery may best be achieved in a multidisciplinary environment involving gastroenterologists, surgeons and radiologists. Patients with CD are now often coming to surgery on at least an immunomodulator, and in our cohort 67.7% on a biologic agent. Recent systematic reviews reported an increase in the post-operative, infective and anastomotic complications in patients on anti-TNFα agents[19,20] which lends further weight for considering earlier surgery.

It is clear that biologic agents improve rates of clinical remission and HRQOL scores in the short

term[21-23]. Long term it is unclear whether they alter disease course. Disease recurrence rates at 5 years were reported at 36.6% with infliximab therapy[24] suggesting that for some the response is short lived for some patients. Resection rates in the literature are contradictory, with some studies reporting a decline in surgical resection[24,25], whilst others have reported no change despite increasing use of biologic agents[6,26-28], which may reflect the use of biologic agents at a later stage in the disease process where fibrosis and scarring predominate over inflammation, reducing their efficacy.

It is worth noting that the European evidence based consensus from the European Crohn's and Colitis Organization recommends resection for patients with ileocolic disease with obstructive symptoms[29]. Silverstein *et al*[30] reported on the high costs associated with surgical intervention, accounting for 44% of the total lifetime health costs (USD17562) in a patient with CD, but also that it offered the longest remissions. However, this study pre-dates the widespread use of biologic agents and the high costs associated with them. A Canadian study estimated a direct health care cost of USD21416 per patient for the first year of Infliximab treatment[31]. No formal cost analysis was performed, however, given the lower proportion of patients requiring medical therapy in the ES cohort, the cost effectiveness of ES *vs* IMT should be explored as, notably 23.8% of the ES cohort avoided the need for ongoing medical therapy altogether.

There are naturally limitations to any retrospective analysis, which prevent strong conclusions being drawn. However, a study prospectively randomizing to early and DS would be difficult to conduct, require long follow up and may not be ethically acceptable. We therefore need to examine real world data such as these whilst taking account of possible sources of bias. Data was not available regarding short term complication rates of surgery and medical therapy so not included in this study. We have used the emergency operation for an acute complication as a surrogate for ES. The phenotypes of the two cohorts are different, however, we feel that the ES group had generally a more aggressive phenotype given then higher proportion of penetrating and stricturing disease presenting with an acute complication requiring resection at index presentation. The younger patients higher proportion of L3 disease in the IMT group reflects a real world cohort with potentially multifocal disease in whom the treating team have adopted medical therapy upfront. However we still believe the groups are comparable as, despite this, the type of surgery and extent of bowel resection are similar between the ES and medically treated cohorts. Our definition of ES is arbitrary, but in six months medical therapy is unlikely to be established. Being a tertiary centre, there is a potential for a referral bias, with less complex disease managed at regional centres.

Our study lends weight to the argument that in selected patients with stricturing or penetrating ileocolonic CD, those undergoing ES may have a more benign disease course, possibly with less need for further surgical intervention and fewer hospital admissions for CD related illness. This is perhaps even more meaningful, given that a significant number of these patients present with aggressive phenotypes requiring ES. Surgery should not be considered as treatment of last resort after all medical therapy has failed. Rather a more considered approach to the timing of resection for symptomatic patients is needed, possibly to achieve longer periods of disease remission with reduced drug exposure and costs to health care.

COMMENTS

Background

Despite the advances in medical therapy for patients Crohn's disease (CD), from the introduction in immunomodulatory agents and biologic agents targeting TNF-α, there has been minimal decline in the rate of surgical resection in these patients. There is evidence in support of an aggressive "top-down" strategy, utilizing more effective agents earlier in the disease course such as the immunomodulators and biologic agents to control the inflammatory process and prevent progression. It must be considered whether a more aggressive approach still, with early surgery (ES) in selected patients may further improve outcomes in these patients.

Research frontiers

The authors in selecting patients with symptomatic ileo-colonic CD, undertaking early surgical resection prior to starting medical therapy for their CD may confer a benefit in the long term, regarding the need for further surgery reduced requirement for medical therapy in maintaining control of their disease.

Innovations and breakthrough

This study supports evidence in the literature that ES may confer a benefit in selected patients with CD, as patients required fewer admissions to hospital, spent fewer total days in hospital by the end of this study period in spite of the inclusion of their index admission for their acute presentation and operation. In addition, the authors found a longer time duration between their index operation and their subsequent operation when compared to those undergoing initial medical therapy.

Applications

Decision making in the management of patients with CD is complex and best undertaken in a multidisciplinary setting. Traditionally surgery has been reserved as an act of last resort. This study suggests a bolder approach may be of benefit in symptomatic patients with ileal or ileocolonic disease.

Peer-review

It is a study about an interesting topic in CD: The effectiveness of ES in avoiding CD recurrence.

REFERENCES

1 **Jeon SJ**, Lee KJ, Lee MH, Lim SK, Kang CJ, Kim JH. Rates of early surgery and associated risk factors in Crohn's disease. *Korean J Gastroenterol* 2010; **56**: 236-241 [PMID: 20962559 DOI: 10.4166/kjg.2010.56.4.236]

2 **Bernell O**, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. *Ann Surg* 2000; **231**: 38-45 [PMID: 10636100 DOI: 10.1097/00000658-200001000-00006]

3 **Golovics PA**, Lakatos L, Nagy A, Pandur T, Szita I, Balogh M, Molnar C, Komaromi E, Lovasz BD, Mandel M, Veres G, Kiss LS,

Vegh Z, Lakatos PL. Is early limited surgery associated with a more benign disease course in Crohn's disease? *World J Gastroenterol* 2013; **19**: 7701-7710 [PMID: 24282358 DOI: 10.3748/wjg.v19.i43.7701]

4 **Loftus EV Jr**, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. *Aliment Pharmacol Ther* 2002; **16**: 51-60 [PMID: 11856078 DOI: 10.1046/j.1365-2036.2002.01140.x]

5 **Greenstein AJ**, Sachar DB, Pasternack BS, Janowitz HD. Reoperation and recurrence in Crohn's colitis and ileocolitis Crude and cumulative rates. *N Engl J Med* 1975; **293**: 685-690 [PMID: 1160935 DOI: 10.1056/NEJM197510022931403]

6 **Cosnes J**, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005; **54**: 237-241 [PMID: 15647188 DOI: 10.1136/gut.2004.045294]

7 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]

8 **Colombel JF**, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65 [PMID: 17241859 DOI: 10.1053/j.gastro.2006.11.041]

9 **Ananthakrishnan AN**, McGinley EL, Binion DG, Saeian K. A nationwide analysis of changes in severity and outcomes of inflammatory bowel disease hospitalizations. *J Gastrointest Surg* 2011; **15**: 267-276 [PMID: 21108015 DOI: 10.1007/s11605-010-1396-3]

10 **Aratari A**, Papi C, Leandro G, Viscido A, Capurso L, Caprilli R. Early versus late surgery for ileo-caecal Crohn's disease. *Aliment Pharmacol Ther* 2007; **26**: 1303-1312 [PMID: 17848181 DOI: 10.1111/j.1365-2036.2007.03515.x]

11 **Latella G**, Cocco A, Angelucci E, Viscido A, Bacci S, Necozione S, Caprilli R. Clinical course of Crohn's disease first diagnosed at surgery for acute abdomen. *Dig Liver Dis* 2009; **41**: 269-276 [PMID: 18955023 DOI: 10.1016/j.dld.2008.09.010]

12 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5A-36A [PMID: 16151544]

13 **Gao X**, Yang RP, Chen MH, Xiao YL, He Y, Chen BL, Hu PJ. Risk factors for surgery and postoperative recurrence: analysis of a south China cohort with Crohn's disease. *Scand J Gastroenterol* 2012; **47**: 1181-1191 [PMID: 22845663 DOI: 10.3109/00365521.2012.668931]

14 **Thirlby RC**, Land JC, Fenster LF, Lonborg R. Effect of surgery on health-related quality of life in patients with inflammatory bowel disease: a prospective study. *Arch Surg* 1998; **133**: 826-832 [PMID: 9711955 DOI: 10.1001/archsurg.133.8.826]

15 **Casellas F**, López-Vivancos J, Vergara M, Malagelada J. Impact of inflammatory bowel disease on health-related quality of life. *Dig Dis* 1999; **17**: 208-218 [PMID: 10754360 DOI: 10.1159/000016938]

16 **Hanauer SB**, Korelitz BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, Present DH. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004; **127**: 723-729 [PMID: 15362027 DOI: 10.1053/j.gastro.2004.06.002]

17 **Yoshida K**, Fukunaga K, Ikeuchi H, Kamikozuru K, Hida N, Ohda Y, Yokoyama Y, Iimuro M, Takeda N, Kato K, Kikuyama R, Nagase K, Hori K, Nakamura S, Miwa H, Matsumoto T. Scheduled infliximab monotherapy to prevent recurrence of Crohn's disease following ileocolic or ileal resection: a 3-year prospective randomized open trial. *Inflamm Bowel Dis* 2012; **18**: 1617-1623 [PMID: 22081474 DOI: 10.1002/ibd.21928]

18 **De Cruz P**, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, Liew D, Prideaux L, Lawrance IC, Andrews JM, Bampton PA, Jakobovits S, Florin TH, Gibson PR, Debinski H, Gearry RB, Macrae FA, Leong RW, Kronborg I, Radford-Smith G, Selby W, Johnston MJ, Woods R, Elliott PR, Bell SJ, Brown SJ, Connell WR, Desmond PV. Efficacy of thiopurines and adalimumab in preventing Crohn's disease recurrence in high-risk patients - a POCER study analysis. *Aliment Pharmacol Ther* 2015; **42**: 867-879 [PMID: 26314275 DOI: 10.1111/apt.13353]

19 **El-Hussuna A**, Theede K, Olaison G. Increased risk of post-operative complications in patients with Crohn's disease treated with anti-tumour necrosis factor α agents - a systematic review. *Dan Med J* 2014; **61**: A4975 [PMID: 25441731]

20 **Yang ZP**, Hong L, Wu Q, Wu KC, Fan DM. Preoperative infliximab use and postoperative complications in Crohn's disease: a systematic review and meta-analysis. *Int J Surg* 2014; **12**: 224-230 [PMID: 24394691 DOI: 10.1016/j.ijsu.2013.12.015]

21 **Feagan BG**, Yan S, Bala M, Bao W, Lichtenstein GR. The effects of infliximab maintenance therapy on health-related quality of life. *Am J Gastroenterol* 2003; **98**: 2232-2238 [PMID: 14572573 DOI: 10.1111/j.1572-0241.2003.07674.x]

22 **Feagan BG**, Panaccione R, Sandborn WJ, D'Haens GR, Schreiber S, Rutgeerts PJ, Loftus EV, Lomax KG, Yu AP, Wu EQ, Chao J, Mulani P. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology* 2008; **135**: 1493-1499 [PMID: 18848553 DOI: 10.1053/j.gastro.2008.07.069]

23 **Loftus EV**, Feagan BG, Colombel JF, Rubin DT, Wu EQ, Yu AP, Pollack PF, Chao J, Mulani P. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol* 2008; **103**: 3132-3141 [PMID: 18853973 DOI: 10.1111/j.1572-0241.2008.02175.x]

24 **Schnitzler F**, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut* 2009; **58**: 492-500 [PMID: 18832518 DOI: 10.1136/gut.2008.155812]

25 **Sakatani A**, Fujiya M, Ito T, Inaba Y, Ueno N, Kashima S, Tominaga M, Moriichi K, Okamoto K, Tanabe H, Ikuta K, Ohtake T, Kono T, Furukawa H, Ashida T, Kohgo Y. Infliximab extends the duration until the first surgery in patients with Crohn's disease. *Biomed Res Int* 2013; **2013**: 879491 [PMID: 24371835]

26 **Lazarev M**, Ullman T, Schraut WH, Kip KE, Saul M, Regueiro M. Small bowel resection rates in Crohn's disease and the indication for surgery over time: experience from a large tertiary care center. *Inflamm Bowel Dis* 2010; **16**: 830-835 [PMID: 19798731 DOI: 10.1002/ibd.21118]

27 **Siassi M**, Weiger A, Hohenberger W, Kessler H. Changes in surgical therapy for Crohn's disease over 33 years: a prospective longitudinal study. *Int J Colorectal Dis* 2007; **22**: 319-324 [PMID: 16733647 DOI: 10.1007/s00384-006-0150-5]

28 **Jones DW**, Finlayson SR. Trends in surgery for Crohn's disease in the era of infliximab. *Ann Surg* 2010; **252**: 307-312 [PMID: 20585239 DOI: 10.1097/SLA.0b013e3181e61df5]

29 **Van Assche G**, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, Guslandi M, Oldenburg B, Dotan I, Marteau P, Ardizzone A, Baumgart DC, D'Haens G, Gionchetti P, Portela F, Vucelic B, Söderholm J, Escher J, Koletzko S, Kolho KL, Lukas M, Mottet C, Tilg H, Vermeire S, Carbonnel F, Cole A, Novacek G, Reinshagen M, Tsianos E, Herrlinger K, Oldenburg B, Bouhnik Y, Kiesslich R, Stange E, Travis S, Lindsay J. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis* 2010; **4**: 63-101 [PMID: 21122490 DOI: 10.1016/j.crohns.2009.09.009]

30 **Silverstein MD**, Loftus EV, Sandborn WJ, Tremaine WJ, Feagan

BG, Nietert PJ, Harmsen WS, Zinsmeister AR. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology* 1999; **117**: 49-57 [PMID: 10381909 DOI: 10.1016/S0016-5085(99)70549-4]

31 **Loomes DE**, Teshima C, Jacobs P, Fedorak RN. Health care resource use and costs in Crohn's disease before and after infliximab therapy. *Can J Gastroenterol* 2011; **25**: 497-502 [PMID: 21912761 DOI: 10.1155/2011/157604]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Aspirin use for primary prophylaxis: Adverse outcomes in non-variceal upper gastrointestinal bleeding

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Data sharing statement: The original anonymous dataset is available on request from the corresponding author, Dr. Kassem A Barada at kb02@aub.edu.lb.

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Abstract

AIM: To compare outcomes of patients with non-variceal upper gastrointestinal bleeding (NVUGIB) taking aspirin for primary prophylaxis to those not taking it.

METHODS: Patients not known to have any vascular disease (coronary artery or cerebrovascular disease) who were admitted to the American University of Beirut Medical Center between 1993 and 2010 with NVUGIB were included. The frequencies of in-hospital mortality, re-bleeding, severe bleeding, need for surgery or embolization, and of a composite outcome defined as the occurrence of any of the 4 bleeding related adverse outcomes were compared between patients receiving aspirin and those on no antithrombotics. We also compared frequency of in hospital complications and length of hospital stay between the two groups.

RESULTS: Of 357 eligible patients, 94 were on aspirin and 263 patients were on no antithrombotics (control

group). Patients in the aspirin group were older, the mean age was 58 years in controls and 67 years in the aspirin group ($P < 0.001$). Patients in the aspirin group had significantly more co-morbidities, including diabetes mellitus and hypertension [25 (27%) *vs* 31 (112%) and 44 (47%) *vs* 74 (28%) respectively, ($P = 0.001$)], as well as dyslipidemia [21 (22%) *vs* 16 (6%), $P < 0.0001$). Smoking was more frequent in the aspirin group [34 (41%) *vs* 60 (27%), $P = 0.02$)]. The frequencies of endoscopic therapy and surgery were similar in both groups. Patients who were on aspirin had lower in-hospital mortality rates (2.1% *vs* 13.7%, $P = 0.002$), shorter hospital stay (4.9 d *vs* 7 d, $P = 0.01$), and fewer composite outcomes (10.6% *vs* 24%, $P = 0.01$). The frequencies of in-hospital complications and re-bleeding were similar in the two groups.

CONCLUSION: Patients who present with NVUGIB while receiving aspirin for primary prophylaxis had fewer adverse outcomes. Thus aspirin may have a protective effect beyond its cardiovascular benefits.

Key words: Aspirin; Morbidity; Mortality; Non-variceal upper gastrointestinal bleeding; Outcomes

Core tip: Aspirin is known to increase the risk of upper gastrointestinal bleeding (UGIB), and it is customary to stop aspirin in patients presenting with gastrointestinal bleeding. Some studies have shown that being on aspirin is associated with better outcome in those patients. Our study compared clinical outcomes in patients who presented with non-variceal UGIB while taking aspirin for primary prophylaxis only to those of patients not taking aspirin. We found that patients taking aspirin had lower mortality and shorter hospital stay than patients not taking aspirin.

Souk KM, Tamim HM, Abu Daya HA, Rockey DC, Barada KA. Aspirin use for primary prophylaxis: Adverse outcomes in non-variceal upper gastrointestinal bleeding. *World J Gastrointest Surg* 2016; 8(7): 501-507 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i7/501.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i7.501

INTRODUCTION

Aspirin is being used widely in primary and secondary prevention of cardiovascular diseases, and it is taken by more than 25%-33% of people older than 65 years[1]. In addition, both individual studies and meta-analysis of trials of anti-platelet therapy indicate that aspirin and other anti-platelet drugs reduce the risk of serious vascular events by approximately 25%[2].

Despite its cardiovascular protection, aspirin is associated with a 2 fold increase in risk of upper gastrointestinal bleeding (UGIB)[3]. However, most studies suggest that aspirin decreases mortality and hospital stay in patients with non-variceal upper gastrointestinal bleeding (NVUGIB)[4,5], while some report no significant effect[6].

We recently reported that being on aspirin on presentation confers protection against mortality and morbidity in peptic disease related-UGIB[7], and in patients with NVUGIB overall[8]. We also reported that in-hospital mortality from cardiovascular causes in patients taking aspirin was similar to controls. Hence, it is not clear if the protective effect of aspirin is due to its known cardiovascular benefits. This study aims to determine if the protective effect of aspirin in NVUGIB persists in patients with no known cardiovascular or cerebrovascular disease. This is done by comparing clinical outcomes in patients presenting with NVUGIB while receiving aspirin as primary prophylaxis to those who are not taking it.

MATERIALS AND METHODS

This was a retrospective cohort study of patients admitted to American University of Beirut Medical Center (AUBMC) with NVUGIB between 1993 and 2010. AUBMC is a tertiary referral medical center that provides health care for around 1.5 million people in Lebanon.

The study was approved by the Institutional Review Board of AUBMC (IM.KB.09).

Inclusion and exclusion criteria

In this study we included all patients who were admitted with hematemesis, coffee ground vomiting, and/or melena in the presence of an identified source of UGIB site on upper gastrointestinal endoscopy[7]. We also considered patients with hematochezia to have UGIB if upper endoscopy showed a source of bleeding and colonoscopy was negative. For patients who didn't have endoscopy, we classified patients as having UGIB if they had coffee ground emesis, hematemesis or melena.

We excluded all patients who presented with melena and/or hematochezia who had a colonic source of bleeding. Patients who met the criteria of UGIB from esophageal/gastric varices and those who had occult gastrointestinal or small bowel bleeding were excluded.

We also excluded all patients with documented history of coronary artery disease, cerebrovascular accident/transient ischemic attack (TIA), peripheral vascular disease, and those on any non-aspirin anti-platelets or anticoagulants.

Data collection

Medical records of patients with signs and symptoms of UGIB were reviewed, using the ICD-9/ICD-10 coding system (codes for the following symptoms: UGIB, melena, hematochezia, hematemesis, coffee ground emesis). The data was collected from charts using a standardized data collection form. During chart review,

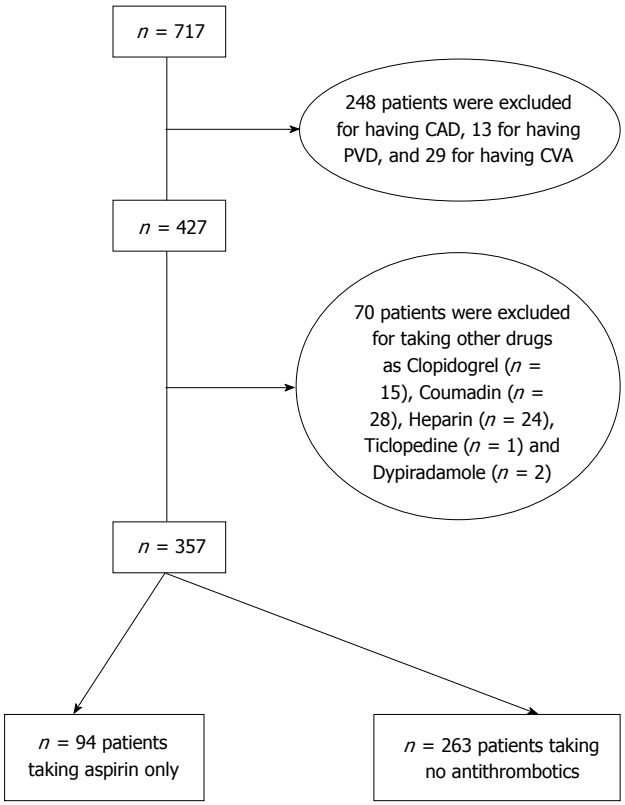

Figure 1 The flow and inclusion/exclusion criteria of patients with non-variceal upper gastrointestinal bleeding in the study. CAD: Coronary artery disease; PVD: Peripheral vascular disease; CVA: Cerebrovascular accident.

we extracted the following information: Patient's age, sex, comorbid conditions (hypertension, diabetes mellitus, renal insufficiency, dyslipidemia, active systemic or gastrointestinal cancer, congestive heart failure, valvular heart disease, atrial fibrillation and deep vein thrombosis); mode of clinical presentation; duration of bleeding; vital signs and initial blood studies obtained upon arrival to the emergency room including complete blood count, international normalized ratio (INR), and prothrombin time; management in the emergency room and the hospital including blood transfusion. We also recorded findings on diagnostic upper gastrointestinal endoscopy and the source of bleeding; type of therapeutic endoscopic procedure undertaken whenever applicable; angiography and embolization, surgical treatment and in hospital mortality. The frequency of the following outcomes were determined: In-hospital mortality, need for surgery, severe bleeding (hypotension with a systolic blood pressure < 90 mmHg on admission, tachycardia with heart rate > 119 beat/min, or transfusion of more than 3 units of packed red blood cells), re-bleeding (re-bleeding after 24 h from the initial endoscopic evaluation) and therapy (recurrence of bleeding within 1 mo from discharge was also considered rebleeding), in-hospital complications including myocardial infarction, angina, deep vein thrombosis, pulmonary embolism, stroke, TIA, pneumonia, urinary tract infection, skin infections, sepsis, acute respiratory distress syndrome, renal failure, need for mechanical ventilation, and disseminated intravascular coagulopathy; duration of hospitalization, need for blood transfusion, and number of blood units transfused were also recorded. The primary outcome was in-hospital mortality. The secondary outcomes included re-bleeding, severe bleeding, need for surgery or embolization, and the occurrence of any bleeding related composite outcome defined as the occurrence of any of the following: In hospital mortality, re-bleeding, severe bleeding, need for surgery or embolization[7]. We also compared in hospital complications and length of hospital stay. We divided the patients into two main groups: Those who were on aspirin upon presentation, and those who were not. We compared all the characteristics and outcomes listed above between the two groups.

Statistical analysis

Data management and analysis were carried out using the Statistical Analysis Software (SAS, version 9.1). Descriptive analyses were carried out by calculating the numbers and percent for categorical variables, and the mean and standard deviation SD for the continuous ones. Bivariate analyses were performed using the χ^2 test or the independent student *t*-test, as appropriate.

To control for the effect of potentially confounding variables, multivariable analyses were carried out while controlling for different risk factors. For categorical outcomes multivariate logistic regression analyses were carried out where the OR, 95%CI, and *P*-value were reported. On the other hand, for continuous variables multivariate linear regression was carried out where the β-coefficient, 95%CI, and *P*-value were reported. Variables included in the regression model were those of either statistical or clinical significance. A P value < 0.05 indicates statistical significance.

RESULTS

Subjects

A total of 1175 patients were admitted with acute gastrointestinal bleeding between 1993 and 2010. Out of the 1175 patients, 717 patients had NVUGIB, of which 357 were included in this study. A total of 94 patients were on aspirin only and 263 patients were on no antithrombotics (control group, Figure 1).

Demographics and clinical characteristics

The mean age was 58 years in controls and 67 years in the aspirin group (P < 0.001). Most patients were males. Patients on aspirin were more likely to have diabetes mellitus and hypertension [25 (27%) *vs* 31 (112%) and 44 (47%) *vs* 74 (28%) respectively, (P = 0.001)], as well as dyslipidemia [21 (22%) *vs* 16 (6%), P < 0.0001]. Smoking was more frequent in the aspirin group [34 (41%) *vs* 60 (27%), P = 0.02] (Table 1).

Controls had a higher prevalence of cancer (20.9% *vs* 6.4%, P < 0.001) and were more likely to have a history of peptic ulcer disease. The use of PPI was

Table 1 Clinical characteristics of patients with non-variceal upper gastrointestinal bleeding in both groups *n* (%)

Group	No anti-thrombotics *n* = 263	Aspirin *n* = 94	*P* value
Age mean (SD)	58.4 (19.1)	66.8 (13.1)	< 0.001
Male gender	169 (64.3)	71 (75.5)	0.05
Smoking	60 (27.0)	34 (41.0)	0.02
Diabetes mellitus	31 (11.8)	25 (26.6)	0.001
Hypertension	74 (28.1)	44 (46.8)	0.001
Dyslipidemia	16 (6.1)	21 (22.3)	< 0.0001
Cancer	55 (20.9)	6 (6.4)	0.001
NSAIDS	47 (17.9)	16 (17.0)	0.85
PPI	29 (11.0)	4 (4.3)	0.05
History of peptic ulcer disease	69 (26.2)	13 (13.8)	0.01

P < 0.05 is considered significant. NVUGIB: Non-variceal upper gastrointestinal bleeding; Aspirin: Aspirin only; No anti-thrombotics: Including clopidogrel, coumadin, heparin, ticlopedine and dypiradamole; SD: Standard deviation; NSAIDS: Non steroidal anti-inflammatory drug; PPI: Proton pump inhibitor.

higher in controls [29 (11%) *vs* 4 (4%), *P* = 0.05] (Table 1). Controls also had a higher INR than patients on aspirin (Table 2).

Presentation and endoscopic findings

Upon presentation, patients in the aspirin group had more syncope and melena, but less hematemesis than controls [21.3% *vs* 12.5%, *P* = 0.04, 51 (54.3%) *vs* 109 (41.4%), *P* = 0.03 and 18.1% *vs* 28.9%, *P* = 0.04, respectively]. Upper gastrointestinal endoscopy was done on 83% of patients in the aspirin group and 71.5% of patients in the control group. The prevalence of peptic lesions found at endoscopy was higher in the aspirin group, including gastric ulcers (28.7% *vs* 15.2%, *P* = 0.004), erosive duodenitis (16% *vs* 5.3%, *P* = 0.001), and erosive gastritis (40.4% *vs* 12.9%, *P* < 0.0001) (Table 2).

In hospital medical and endoscopic management

The percentage of patients transfused with blood was similar in both groups, 70.2% in aspirin *vs* 61.2% in control (*P* = 0.12); and the average was 4 units of packed red blood cells per transfused patient. In both groups, the frequencies of endoscopic therapy and surgery were similar (Table 2).

Outcomes

After adjusting for age and comorbidities (congestive heart failure, systemic cancer, diabetes mellitus, chronic renal failure), patients on aspirin were less likely to die in-hospital (OR = 0.15, 95%CI: 0.03-0.64, *P* = 0.002), less likely to experience the composite outcome (OR = 0.42, 95%CI: 0.20-0.89, *P* = 0.01), and tended to have a shorter hospital stay (4.9 d *vs* 7 d, *P* = 0.01) compared to controls. However, they had similar rates of in-hospital complications, re-bleeding and severe bleeding (Table 3).

Table 2 Association between aspirin use and presentation/ management *n* (%)

Group	No anti-thrombotics *n* = 263	Aspirin *n* = 94	*P* value
Melena	109 (41.4)	51 (54.3)	0.03
Hematemesis	76 (28.9)	17 (18.1)	0.04
Hematemesis + Melena	46 (17.5)	16 (17.05)	0.92
Hematochezia	8 (3.0)	2 (2.1)	0.48
Syncope	33 (12.5)	20 (21.3)	0.04
Hgb, g/L, mean (SD)	9.2 (2.8)	9.1 (2.4)	0.80
Hct, (%), mean (SD)	27.4 (8.2)	27.0 (7.1)	0.70
INR, mean (SD)	1.2 (0.7)	1.0 (0.2)	0.003
Gastric ulcers	40 (15.2)	27 (28.7)	0.004
Duodenal ulcers	65 (24.7)	31 (33.0)	0.12
Erosive esophagitis	31 (11.8)	10 (10.6)	0.76
Erosive gastritis	34 (12.9)	38 (40.4)	< 0.0001
Erosive duodenitis	14 (5.3)	15 (16.0)	0.001
Mallory Weiss	18 (6.8)	4 (4.3)	0.37
Hiatal Hernia	24 (9.1)	11 (11.7)	0.47
AVM	11 (4.2)	3 (3.2)	0.47
Cancer	6 (2.3)	0 (0.0)	0.16
Transfusion-unit Mean (SD)	4.7 (5.5)	4.0 (3.8)	0.25
Transfusion %	161 (61.2)	66 (70.2)	0.12
Thermal coagulation	25 (9.5)	14 (14.9)	0.15
Hemostatic clips	2 (0.8)	0 (0.0)	0.54
Argon-plasma coagulation	4 (1.5)	2 (2.1)	0.50
Angiography-embolization	1 (0.4)	0 (0.0)	0.74
Surgery	21 (8.0)	5 (5.3)	0.39

P < 0.05 is considered significant. NVUGIB: Non-variceal upper gastrointestinal bleeding; Aspirin: Aspirin only; No anti-thrombotics: Including clopidogrel, coumadin, heparin, ticlopedine and dypiradamole; SD: Standard deviation; Hgb: Hemoglobin; Hct: Hematocrit; INR: International normalized ratio; AVM: Arteriovenous malformation; Surgery as any type of surgical procedure performed to control gastrointestinal bleeding.

Because the prevalence of cancer was higher in the control group, we did a multivariate analysis in which cancer was considered a covariate rather than one of the comorbidities. The protective effect of aspirin against in hospital mortality remained unchanged.

As there were some patients who did not have endoscopy, a multivariate analysis was done on patients who had endoscopy. Regarding the mortality, it was significantly lower with aspirin group *vs* non aspirin OR: 0.68, 95%CI: 0.63-0.74; but this difference was not seen with severe bleeding OR = 1.03, 95%CI: 0.69-1.52 and rebleeding OR = 1.51, 95%CI: 0.67-3.39.

DISCUSSION

Our study suggests that patients without known vascular disease who present with NVUGIB while taking aspirin appear to have better outcomes than patients not taking any antithrombotics. Specifically, these patients had lower mortality and morbidity, and shorter hospital stay than patients not on antithrombotics.

It is known that patients who have more than one risk factor for developing vascular events are more likely to use aspirin as primary prophylaxis[9]. In this

Table 3 Multivariate analyses of the outcomes in aspirin users *vs* non users

Group	No anti-thrombotics *n* = 263	Aspirin *n* = 94	*P* value	Crude OR (95%CI)	Adjusted OR (95%CI)
Mortality	36 (13.7)	2 (2.1)	0.002	0.14 (0.03-0.58)	0.15 (0.03-0.64)
Hospital stay (d) Mean (SD)	7.0 (10.3)	4.9 (3.5)	0.01		
Complications-Thrombo-embolic	3 (1.1)	3 (3.2)	0.19	2.86 (0.57- 14.41)	4.79 (0.77-29.96)
Complications-infection[1]	40 (15.2)	14 (14.9)	0.94	0.98 (0.50-1.89)	0.90 (0.45-1.81)
Complications-respiratory[2]	15 (5.7)	3 (3.2)	0.42	0.55 (0.15-1.93)	0.58 (0.15-2.19)
Complications-myocardial infarction	3 (1.1)	1 (1.1)	1	0.93 (0.10-9.07)	0.68 (0.07-6.79)
Complications-renal failure	30 (11.4)	9 (9.6)	0.63	0.82 (0.38-1.80)	0.68 (0.30-1.55)
Complications-DIC	7 (2.7)	0 (0.0)	0.2		
All in hospital complications	79 (30.0)	26 (27.7)	0.66	0.89 (0.53-1.50)	0.76 (0.43-1.32)
Composite outcome[3]	63 (24.0)	10 (10.6)	0.01	0.38 (0.19-0.77)	0.42 (0.20-0.89)
Severe hemorrhage	97 (36.9)	37 (39.4)	0.67	1.11 (0.69-1.80)	1.18 (0.70-1.99)
Re-bleeding	5 (5.3)	27 (10.3)	0.15	0.49 (0.18-1.32)	0.42 (0.15-1.19)

[1]Complications-infection composite: Including pneumonia, aspiration pneumonia, sepsis, urinary tract infection, skin infection; [2]Complications-respiratory composite: Including ARDS and mechanical ventilation; [3]Composite outcome include mortality, severe bleeding, re-bleeding, need for surgery or embolization. Severe hemorrhage was defined as BP < 90 mmHg, HR > 120 b/min, Hb < 7 g/dL on presentation, or transfusion of > 3 units of blood during hospitalization; rebleeding was defined as recurrence of hematemesis, coffee ground emesis, or melena occurring after 24 h from initial endoscopic evaluation and/or hemostatic therapy and initial stabilization, accompanied by either a decrease in hemoglobin concentration of at least 2 g/L or change in vital signs. $P < 0.05$ is considered significant. Aspirin: Aspirin only; No anti-thrombotics: Including clopidogrel, coumadin, heparin, ticlopedine and dypiradamole; OR: Odds ratio; DIC: Disseminated intravascular coagulation.

study, patients on aspirin were older and had more co-morbidity, yet they had lower mortality rates compared to controls. This occurred even though both groups had similar frequencies of therapeutic endoscopic procedures, arterial embolization and surgery making it unlikely that those contributed to the better outcome in the aspirin group. Thus, the contribution of this study is that aspirin's beneficial effect in NVUGIB appears to extend to patients not known to have vascular disease.

It has been previously reported that patients with UGIB receiving or maintained on aspirin had improved outcomes. For example, in a randomized trial of aspirin *vs* placebo in patients who presented with peptic ulcer bleeding while taking aspirin, half of the deaths in the placebo group were due to non-cardiovascular causes, further suggesting that aspirin's protective effect is not solely due to its cardiovascular benefits[10]. In two relatively large Italian prospective database studies, use of low dose aspirin upon presentation with UGIB was an independent predictor of better outcome including lower 30-d mortality[11,12]. This was true for both outpatient and inpatient NVUGIB. Furthermore, in a large pan-European retrospective cohort, it was reported that use of low or high dose aspirin was an independent predictor of lower 30 d mortality in NVUGIB[13]. Finally, in a retrospective cohort of 766 patients with UGIB due to peptic ulcers, it was reported that patients using aspirin upon presentation had a markedly decreased risk of fatal outcome (OR = 0.12, 95%CI: 0.012-0.67)[6]. Thus, the protective effect of aspirin seems to hold true for both low and high dose aspirin, and seems to cover patients with peptic ulcer related and non-peptic ulcer related NVUGIB. However, in the studies mentioned above, it was not clear whether control patients were taking other antithrombotics, and whether patients taking aspirin were using other antithrombotics concomitantly. Furthermore, in none of them was a cause of death analysis undertaken to determine how aspirin exerted its protective effect. In contrast, three studies reported no effect of aspirin on mortality in patients with UGIB. In a prospective observational study of 392 patients there was no effect of antiplatelet therapy (aspirin and/or clopidogrel) on re-bleeding, urgent surgery or mortality[14]. In another study, patients using aspirin/NSAIDs had similar mortality to those not using them. Finally, it was reported that aspirin users had lower 30-d mortality than controls among 7204 patients with peptic ulcer bleeding, but this was of borderline significance[5]. To our knowledge, there are no studies showing that aspirin increases mortality in NVUGIB.

Controls in our study had a higher prevalence of systemic cancer. In order to determine if cancer could explain, in part, the high mortality in controls, we conducted two multivariate analyses, one in which the presence of cancer was included in the composite comorbidity score, and another one in which cancer was considered a covariate. The analysis revealed that the protective effect of aspirin against in-hospital mortality remained unchanged[8].

The mechanism for the lower rate of bleeding related hospital complications and mortality is open to speculation. Aspirin is a non-steroidal anti-inflammatory drug with inhibitory effects on cyclo-oxygenases (COX). COX inhibition has vasoconstrictive and anti-natriuretic effects, which are mediated by inhibition of prostaglandin E-2 and prostacyclin synthesis[15]. Aspirin has been reported to inhibit nitric oxide synthesis, which in turn inhibit vasodilatation[16]. By constricting the vessels in the gastrointestinal system, it may decrease the severity of NVUGIB. We recognize limitations in our study. Patients with risk factors for vascular disease were not excluded, and therefore some of our patients could

have occult or latent vascular disease where aspirin protects this population against in hospital complications and mortality. The study design is not prospective or a randomized controlled trial. It is a single institution study and the sample size was small, so the applicability of the findings to other populations requires further testing. We do not have long term follow up on our patients and not all patients had endoscopy. Furthermore, the Forrest classification of bleeding lesions was not documented on all patients, which is a limitation of our study. Finally, the control group had higher INR level which may increase the risk of adverse outcomes. However, our study has several strengths. First, this is the first study to examine the effect of aspirin use as primary prophylaxis on clinical outcomes in patients with NVUGIB. Second, data collection was performed using the ICD-9 codes resulting in the identification of all the potential cases of UGIB, after which each case was reviewed individually by using well developed criteria. Finally, the study was conducted in a tertiary care referral center where all diagnostic and therapeutic procedures are standardized.

In conclusion, aspirin used for primary prophylaxis has a protective effect against adverse outcomes in patients admitted with NVUGIB, and this benefit probably extends beyond its known cardio-protective effect. Further prospective and randomized controlled trials are needed to validate these findings.

COMMENTS

Background

Aspirin is being widely used as primary and secondary prophylaxis for cardiovascular disease. However, aspirin use is associated with a 2 fold increase in risk of upper gastrointestinal bleeding (UGIB).

Research frontiers

Most studies suggest that aspirin decreases mortality and hospital stay in patients with non-variceal upper gastrointestinal bleeding (NVUGIB), while some report no significant effect. However, these studies included patients using aspirin as secondary prophylaxis.

Innovations and breakthroughs

In this study the authors compared clinical outcomes in patients that presented with NVUGIB while taking aspirin for primary prophylaxis to those of patients not taking aspirin. The authors found that the use of aspirin was associated with a better outcome, less mortality and shorter in-hospital stay.

Applications

The findings may have an impact on the practice of discontinuing aspirin in patients presenting with NVUGIB, even in those taking it for primary prophylaxis.

Terminology

Aspirin use as primary prophylaxis is defined as the use of aspirin in patients with no documented cardiovascular or cerebrovascular disease.

Peer-review

This is an interesting retrospective study comparing aspirin use with none and the outcomes of NVUGIB. The better results with aspiring use are surprising despite having patients with a poorer overall status compared to the control group.

REFERENCES

1 **Barada K**, Abdul-Baki H, El Hajj II, Hashash JG, Green PH. Gastrointestinal bleeding in the setting of anticoagulation and antiplatelet therapy. *J Clin Gastroenterol* 2009; **43**: 5-12 [PMID: 18607297 DOI: 10.1097/MCG.0b013e31811edd13]

2 **Antithrombotic Trialists Collaboration**. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71-86 [PMID: 11786451 DOI: 10.1136/bmj.324.7329.71]

3 **Hallas J**, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM, Andersen M, Lassen AT. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. *BMJ* 2006; **333**: 726 [PMID: 16984924 DOI: 10.1136/bmj.38947.697558.AE]

4 **van Leerdam ME**, Vreeburg EM, Rauws EA, Geraedts AA, Tijssen JG, Reitsma JB, Tytgat GN. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. *Am J Gastroenterol* 2003; **98**: 1494-1499 [PMID: 12873568 DOI: 10.1111/j.1572-0241.2003.07517.x]

5 **Mose H**, Larsen M, Riis A, Johnsen SP, Thomsen RW, Sørensen HT. Thirty-day mortality after peptic ulcer bleeding in hospitalized patients receiving low-dose aspirin at time of admission. *Am J Geriatr Pharmacother* 2006; **4**: 244-250 [PMID: 17062325]

6 **Åhsberg K**, Höglund P, Staël von Holstein C. Mortality from peptic ulcer bleeding: the impact of comorbidity and the use of drugs that promote bleeding. *Aliment Pharmacol Ther* 2010; **32**: 801-810 [PMID: 20653635 DOI: 10.1111/j.1365-2036.2010.04399.x]

7 **Abu Daya H**, Eloubeidi M, Tamim H, Halawi H, Malli AH, Rockey DC, Barada K. Opposing effects of aspirin and anticoagulants on morbidity and mortality in patients with upper gastrointestinal bleeding. *J Dig Dis* 2014; **15**: 283-292 [PMID: 24593260 DOI: 10.1111/1751-2980.12140]

8 **Wehbeh A**, Tamim HM, Abu Daya H, Abou Mrad R, Badreddine RJ, Eloubeidi MA, Rockey DC, Barada K. Aspirin Has a Protective Effect Against Adverse Outcomes in Patients with Nonvariceal Upper Gastrointestinal Bleeding. *Dig Dis Sci* 2015; **60**: 2077-2087 [PMID: 25732717 DOI: 10.1007/s10620-015-3604-1]

9 **Pearson TA**, Palaniappan LP, Artinian NT, Carnethon MR, Criqui MH, Daniels SR, Fonarow GC, Fortmann SP, Franklin BA, Galloway JM, Goff DC, Heath GW, Frank AT, Kris-Etherton PM, Labarthe DR, Murabito JM, Sacco RL, Sasson C, Turner MB. American Heart Association Guide for Improving Cardiovascular Health at the Community Level, 2013 update: a scientific statement for public health practitioners, healthcare providers, and health policy makers. *Circulation* 2013; **127**: 1730-1753 [PMID: 23519758 DOI: 10.1161/CIR.0b013e31828f8a94]

10 **Sung JJ**, Lau JY, Ching JY, Wu JC, Lee YT, Chiu PW, Leung VK, Wong VW, Chan FK. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2010; **152**: 1-9 [PMID: 19949136 DOI: 10.7326/0003-4819-152-1-201001050-00179]

11 **Marmo R**, Koch M, Cipolletta L, Capurso L, Grossi E, Cestari R, Bianco MA, Pandolfo N, Dezi A, Casetti T, Lorenzini I, Germani U, Imperiali G, Stroppa I, Barberani F, Boschetto S, Gigliozzi A, Gatto G, Peri V, Buzzi A, Della Casa D, Di Cicco M, Proietti M, Aragona G, Giangregorio F, Allegretta L, Tronci S, Michetti P, Romagnoli P, Piubello W, Ferri B, Fornari F, Del Piano M, Pagliarulo M, Di Mitri R, Trallori G, Bagnoli S, Frosini G, Macchiarelli R, Sorrentini I, Pietrini L, De Stefano S, Ceglia T, Chiozzini G, Salvagnini M, Di Muzio D, Rotondano G. Predicting mortality in non-variceal upper gastrointestinal bleeders: validation of the Italian PNED Score and Prospective Comparison with the Rockall Score. *Am J Gastroenterol* 2010; **105**: 1284-1291 [PMID: 20051943 DOI: 10.1038/ajg.2009.687]

12 **Rotondano G**, Cipolletta L, Koch M, Bianco MA, Grossi E, Marmo R. Predictors of favourable outcome in non-variceal upper gastrointestinal bleeding: implications for early discharge? *Dig Liver Dis* 2014; **46**: 231-236 [PMID: 24361122 DOI: 10.1016/j.

dld.2013.10.017]
13 **Lanas A**, Aabakken L, Fonseca J, Mungan ZA, Papatheodoridis GV, Piessevaux H, Cipolletta L, Nuevo J, Tafalla M. Clinical predictors of poor outcomes among patients with nonvariceal upper gastrointestinal bleeding in Europe. *Aliment Pharmacol Ther* 2011; **33**: 1225-1233 [PMID: 21480935]
14 **Ortiz V**, Ortuño J, Rodríguez-Soler M, Iborra M, Garrigues V, Ponce J. Outcome of non-variceal acute upper gastrointestinal bleeding in patients with antithrombotic therapy. *Digestion* 2009; **80**: 89-94 [PMID: 19828953 DOI: 10.1159/000219345]
15 **Messerli FH**. Aspirin: a novel antihypertensive drug? Or two birds with one stone? *J Am Coll Cardiol* 2005; **46**: 984-985 [PMID: 16168279 DOI: 10.1016/j.jacc.2005.06.050]
16 **Amin AR**, Attur MG, Pillinger M, Abramson SB. The pleiotropic functions of aspirin: mechanisms of action. *Cell Mol Life Sci* 1999; **56**: 305-312 [PMID: 11212358 DOI: 10.1007/s000180050432]

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ORIGINAL ARTICLE

Retrospective Study

What operation for recurrent rectal prolapse after previous Delorme's procedure? A practical reality

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Author contributions: Javed MA carried out the acquisition, analysis and interpretation of data and writing the manuscript; Afridi FG contributed to the initial acquisition and analysis of data; Artioukh DY carried out treatment of all patients, study conception and design, acquisition and interpretation of data, editing and final approval of the manuscript.

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Informed consent statement: The study did not require a specific consent apart from informed written consent obtained from each patient at the time of procedure.

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Data sharing statement: The original anonymous dataset is available from the corresponding author at dmitri.artioukh@nhs.net. No additional data are available.

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Abstract

AIM: To report our experience with perineal repair (Delorme's procedure) of rectal prolapse with particular focus on treatment of the recurrence.

METHODS: Clinical records of 40 patients who underwent Delorme's procedure between 2003 and 2014 were reviewed to obtain the following data: Gender; duration of symptoms, length of prolapse, operation time, ASA grade, length of post-operative stay, procedure-related complications, development and treatment of recurrent prolapse. Analysis of post-operative complications, rate and time of recurrence and factors influencing the choice of the procedure for recurrent disease was conducted. Continuous variables were expressed as the median with interquartile range (IQR). Statistical analysis was carried out using the Fisher exact test.

RESULTS: Median age at the time of surgery was 76 years (IQR: 71-81.5) and there were 38 females and 2 males. The median duration of symptoms was 6 mo (IQR: 3.5-12) and majority of patients presented electively whereas four patients presented in the emergency department with irreducible rectal prolapse. The median length of prolapse was 5 cm (IQR: 5-7), median operative time was 100 min (IQR: 85-120) and median post-operative stay was 4 d (IQR: 3-6). Approximately

16% of the patients suffered minor complications such as - urinary retention, delayed defaecation and infected haematoma. One patient died constituting post-operative mortality of 2.5%. Median follow-up was 6.5 mo (IQR: 2.15-16). Overall recurrence rate was 28% (*n* = 12). Recurrence rate for patients undergoing an urgent Delorme's procedure who presented as an emergency was higher (75.0%) compared to those treated electively (20.5%), *P* value 0.034. Median time interval from surgery to the development of recurrence was 16 mo (IQR: 5-30). There were three patients who developed an early recurrence, within two weeks of the initial procedure. The management of the recurrent prolapse was as follows: No further intervention (*n* = 1), repeat Delorme's procedure (*n* = 3), Altemeier's procedure (*n* = 5) and rectopexy with faecal diversion (*n* = 3). One patient was lost during follow up.

CONCLUSION: Delorme's procedure is a suitable treatment for rectal prolapse due to low morbidity and mortality and acceptable rate of recurrence. The management of the recurrent rectal prolapse is often restricted to the pelvic approach by the same patient-related factors that influenced the choice of the initial operation, *i.e.*, Delorme's procedure. Early recurrence developing within days or weeks often represents a technical failure and may require abdominal rectopexy with faecal diversion.

Key words: Rectal prolapse; Recurrence; Perineal repair; Delorme's procedure

Core tip: Delorme's procedure is an attractive and often the only treatment of rectal prolapse available to elderly individuals who often have no physiological reserves to withstand abdominal rectopexy. The management of the recurrent disease is frequently restricted to the perineal approach by the same patient-related factors that limited the choice of the initial operation. Early recurrence developing within days or weeks is difficult to treat and in sufficiently fit patients may require abdominal rectopexy combined with faecal diversion.

Javed MA, Afridi FG, Artioukh DY. What operation for recurrent rectal prolapse after previous Delorme's procedure? A practical reality. *World J Gastrointest Surg* 2016; 8(7): 508-512 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i7/508.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i7.508

INTRODUCTION

Full-thickness prolapse of the rectum is defined as a complete protrusion of the rectal wall through the anus. Although benign, the disease can be debilitating and affect patients' quality of life. The incidence of rectal prolapse is reported as 10 per 1000 in patients aged over 65 years[1] and the majority of affected individuals (80%-95%) are women.

More than 130 surgical operations have been described to treat the prolapse which can broadly be classified into perineal and abdominal procedures, indicating that none is entirely satisfactory[2]. Perineal repair of rectal prolapse, as we understand it now, was named after Edmond Delorme - a French military surgeon who described a technique of mucosal stripping for treatment of procidentia in 1899[3]. It gained popularity and today remains the most frequently used type of perineal procedure. In elderly patients with significant co-morbidities Delorme's is often a first choice procedure being the least invasive and, therefore, carrying less of surgical and anaesthetic risks. The perceived disadvantage of Delorme's procedure is high rates of prolapse recurrence making it sub-optimal operation for young and healthy patients who are able to withstand abdominal rectopexy[4]. The choice of the procedure to deal with the recurrent rectal prolapse is often even more difficult due to the absence of established consensus among colorectal surgeons or guidelines to support decision-making process.

The primary aim of this study was to analyse our experience with the treatment of recurrent rectal prolapsed after failed perineal repair (Delorme's procedure) and, in particular, factors that influenced further management. We also report our experience with Delorme's procedure as a treatment of primary rectal prolapse.

MATERIALS AND METHODS

This was a retrospective observational study where we identified 40 consecutive cases of patients who underwent perineal repair of rectal prolapse (Delorme's procedure) by one specialist team (DYA) in Southport and Ormskirk Hospital and Renacres Hospital between 2003 and 2014. Only patients who underwent Delorme's operation as the first procedure undertaken by the team were included. Patients undergoing all other types of perineal procedures, such as excision of mucosal prolapse and perineal recto-sigmoidectomy (Altemier's procedure) were excluded. All patient records were analysed to obtain the following data: Gender; duration of symptoms, length of prolapse, operation time, ASA grade, length of post-operative stay, procedure-related complications, development and treatment of recurrent prolapse and factors influencing the choice of the procedure for recurrent disease. Post-operative complications were classified according to the Clavien-Dindo classification[5]. The last follow-up date was considered as the date of the last documented physical examination. Treatment algorithm used for management of recurrent rectal prolapse is shown in Figure 1.

Statistical analysis

Continuous variables were expressed using non-

Table 1 Patients' demographics

Variables	Values
Median age (yr) (IQR)	76 (71-81.5)
Median ASA score (IQR)	3 (2-3)
Male (*n*)	2
Females (*n*)	38
Median duration of symptoms (mo), (IQR)	6 (3.5-12)

IQR: Interquartile range; ASA: American society of anesthesiologists.

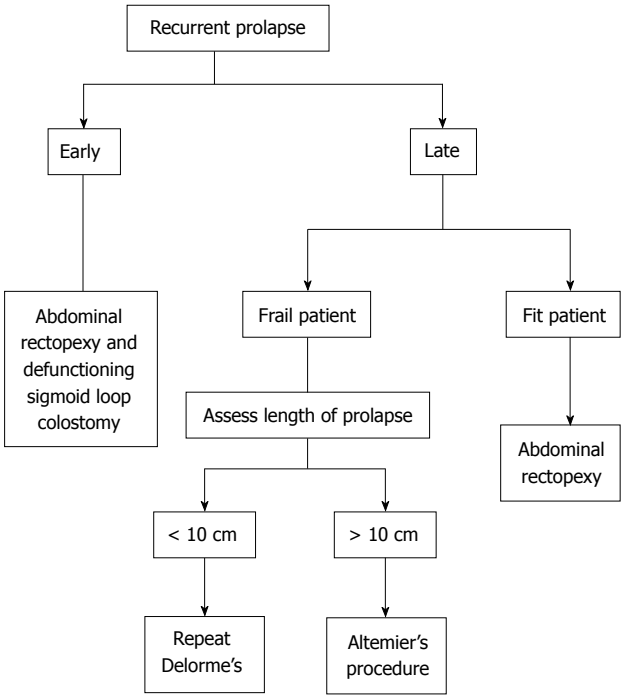

Figure 1 Treatment algorithm for management of recurrent rectal prolapse.

Table 2 Peri-operative data and follow up

Variables	Values
Median length of prolapse (cm) (IQR)	5 (5-7)
Median operative time (min) (IQR)	100 (85-120)
Median post op stay (d) (IQR)	4 (3-6)
Post op complications	Clavien-Dindo
	1 - 6
	2 - 1
	3 - 0
	4a - 1
Median follow up (mo) (IQR)	6.5 (2.15-16)
Median duration of recurrence (mo), (IQR)	16 (5-30)

IQR: Interquartile range.

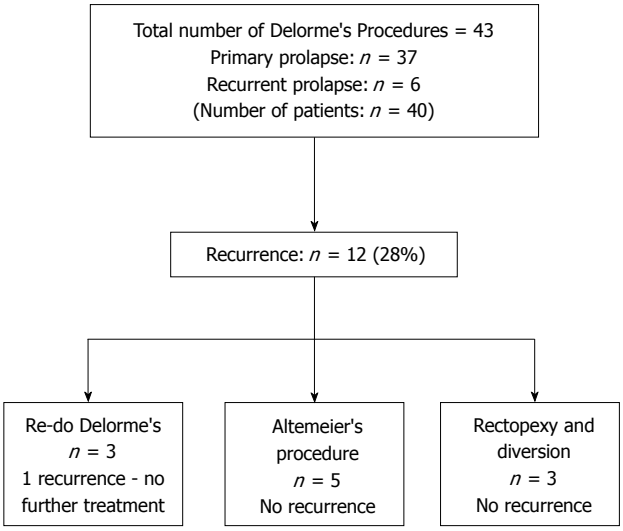

Figure 2 Summary of outcomes in patients undergoing Delorme's procedure for the treatment of full thickness rectal prolapse.

parametric statistics, median with interquartile range (IQR), due to small sample size. Statistical analysis was carried out using the Fischer exact test. Results were considered significant with a probability value of $P < 0.05$. All calculations were performed using Origin software (OriginPro 9). Statistical methods used in the study were independently evaluated by an expert in Biomedical Statistics.

RESULTS

There were 38 females and 2 males in our cohort with the median age of 76 years (IQR: 71-81.5) at the time of surgery (Table 1). The median duration of symptoms was 6 mo (IQR: 3.5-12). Thirty six patients presented electively whereas four patients presented in the emergency department with irreducible rectal prolapse. The median length of prolapse was 5 cm (IQR: 5-7), median operative time was 100 min (IQR: 85-120) and median post-operative stay was 4 d (IQR: 3-6). The majority of patients had no post-operative complications, seven (16%) suffered minor complications, *i.e.*, grade 1 or 2 such as - urinary retention, delayed defaecation and infected haematoma - as defined by Clavien-Dindo classification. One patient died of pneumonia and congestive cardiac failure due to ischaemic heart disease, constituting post-operative mortality of 2.5%. Median follow-up was 6.5 mo (IQR: 2.15-16). Surgical morbidity was higher in patients undergoing surgery for recurrent rectal prolapse (2/7, 28.5%) *vs* primary Delorme's (4/36, 11.1%), *P* value 0.004, and the only mortality in the case series was that of a patient who had surgery for recurrent prolapse. Peri-operative and follow up data are shown in Table 2. Median duration of follow-up was 6.5 mo (range from 2 to 16 mo), the overall recurrence rate was 28% (*n* = 12). A summary of patients' outcome is shown in Figure 2. Recurrence rate for patients undergoing an urgent Delorme's procedure who presented as an emergency was higher (3/4, 75%) compared to those treated electively (9/39, 23%), *P* value 0.034. No other factors included in the analysis were identified to be statistically significant predictors of recurrence. Median duration of recurrence was 16 mo (IQR: 5-30) and there were three patients who developed an early recurrence, within two weeks of the initial procedure. The manage-

ment of the recurrent prolapse was as follows: No further intervention (n = 1), repeat Delorme's (n = 3), Altemeier's procedure (n = 5) and rectopexy with faecal diversion (n = 3). One patient was lost during follow up.

DISCUSSION

Rectal prolapse is a profoundly disabling condition which in Western populations occurs predominantly in elderly women. Surgery is the only way to address the pathology but the choice of operation can be influenced by patient, surgeon and disease-related factors. Traditionally abdominal rectopexy was advocated in young and fit patients and perineal procedures, including Delorme's, were reserved for elderly individuals who are less likely to tolerate abdominal intervention. With introduction of minimally invasive laparoscopic approach many surgeons argue that abdominal rectopexy can be safely applied in most patients with better recurrence-free outcome and minimal long-term complications such as constipation. The advantage of Delorme's procedure is that it combines minimal morbidity and shorter hospital stay with acceptable functional outcome and recurrence rate. Thus, the results of PROSPER trial, the largest randomised controlled trial comparing perineal with abdominal approaches in 293 patients, showed that there was no significant difference in recurrence rates, bowel function or quality of life between any of the treatments. Interestingly, abdominal surgery arm had the rate of recurrence much higher than previously published[6]. Delorme's is an alternative to abdominal rectopexy not only in elderly but also in patients with a short prolapse and those wishing to avoid abdominal intervention[7]. It is therefore not surprising that perineal procedures (Delorme's and Altemeier's) comprise 50% to 60% of all operations performed for rectal prolapse[8]. In our series Delorme's operation was the preferred strategy for treatment unless the length of the prolapse (more than 10 cm) necessitated its resection either perineally (Altemeier's procedure) or abdominally (resection rectopexy). The overall recurrence rate in our cohort was 28% which may seem high in comparison with 20% based on the results of a meta-analysis[9]. Sub-group analysis of electively operated patients, following exclusion of those who had urgent surgery for irreducible prolapse, reveals a recurrence rate of 18.6%. The vast majority (80%) of our patients had no post-operative complications. The only patient who died in our cohort suffered an early recurrence and had little choice but to accept abdominal rectopexy with de-functioning sigmoid loop colostomy. She developed congestive cardiac failure and pneumonia and died on the 43rd day after the second abdominal procedure, thus confirming limited physiological reserves (ASA-3) that influenced the initial choice of perineal repair.

The best management of recurrent rectal prolapse remains uncertain[10] and there are few publications addressing this issue. A recent systematic review evaluating the results of abdominal or perineal surgery for recurrent rectal prolapse, undertaken with the aim of developing an evidence-based treatment algorithm was unable to formulate one due to the variation in surgical techniques and heterogeneity in the quality of studies[10]. Steele *et al*[11] advise that abdominal repair of recurrent rectal prolapse should be undertaken if the patient's risk profile permits. In our experience the same clinical factors, *i.e.*, lack of physiological reserves, restricted repeat surgery to perineal approach exactly as they had done at the time of the initial operation. Delorme's procedure, however, can be safely repeated. When the length of the prolapsed bowel precluded its successful plication our preferred alternative was perineal recto-sigmoidectomy (Altemeier's procedure) which was successfully performed in almost half of recurrences. Figure 1 outlines the algorithm we have adopted for the management of recurrent rectal prolapse after failed Delorme's procedure. We echo the opinion of Pikarskey *et al*[12] that outcome of surgery for rectal prolapse is similar in cases of primary or recurrent prolapse. Early recurrence often represents a technical failure in the background of generalised pelvic floor weakness. In three of our patients it happened on day 7, 10 and 14 after Delorme's procedure due to "cheese-wiring" of plicating sutures and the prolapsed demucosed and inflamed rectum proved particularly difficult to manage. We chose to address it by urgent laparotomy, posterior rectopexy without incorporation of synthetic mesh and formation of defunctioning loop colostomy. This was the only practical choice as the defunctioning stoma offered the benefit of faecal diversion in conditions of rectal inflammation, served as an additional point of bowel fixation anteriorly to the abdominal wall and addressed the likely faecal incontinence in the conditions of generalised pelvic floor weakness.

Our study, being retrospective observational in its design, has inevitable limitations in comparison with a randomised controlled trial. However, a randomised controlled trail aimed to answer some of the questions that have been raised in this paper such as, for example, the best treatment of early post-operative recurrence after failed Derome's procedure may prove to be difficult, if not impossible, to set up.

Delorme's procedure is a suitable treatment in the majority of patients with rectal prolapse regardless the age. It is an attractive choice due to low morbidity and mortality and has acceptable rate of recurrence, at least in the elective setting. The management of the recurrent rectal prolapse is often restricted to the pelvic approach by the same patient-related factors that influenced the choice of the initial operation, *i.e.*, Delorme's procedure. In the event of late recurrence Delorme's procedure can be easily repeated. Long recurrent prolapse requires resection and is best addressed by perineal recto-sigmoidectomy (Altemeier's procedure). Early recurrence developing within days or weeks often represents a technical failure that is difficult to treat and in sufficiently fit patients may require abdominal rectopexy combined

with faecal diversion.

COMMENTS

Background

Many surgical procedures have been described for treatment of full-thickness rectal prolapse indicating that none of them is entirely satisfactory. The choice of the procedure to deal with the recurrent prolapse is even more difficult due to the absence of established consensus among surgeons.

Research frontiers

At present there is insufficient evidence to formulate guidance on the management of the recurrent rectal prolapse as the outcome of such treatment depends on multiple patient and disease-related factors that are often beyond surgeons' control. There is also not enough knowledge to answer the question about the best treatment of early recurrence developing in the immediate post-operative period after failed Delorme's procedure. This study was aimed to assess the outcome of treatment of recurrent rectal prolapse after previous perineal repair (Delorme's procedure) and, in particular, factors that influenced decision-making process. The authors also report their experience of Delorme's procedure as a treatment of primary rectal prolapse.

Innovations and breakthroughs

This retrospective observational study challenges the view that patients with recurrent rectal prolapse after previous Delorme's procedure can be best served with abdominal rectopexy. Despite the perceived better recurrence-free outcome of abdominal interventions the practical reality is that the vast majority of such patients cannot have abdominal rectopexy for the same patient-related reasons why it could be carried out in the first instance. This study also attempts to address the management of the difficult clinical problem of recurrence developing in the early post-operative period after failed Delorme's procedure. In such a scenario the reported experience with urgent laparotomy and posterior suture rectopexy combined with defunctioning sigmoid loop colostomy is encouraging.

Applications

This study may assist surgeons in making decisions about the management of recurrent rectal prolapse. Future studies on the treatment of early post-operative recurrence will be of potential interest.

Terminology

The term rectal prolapse refers to a full-thickness (or complete) protrusion of the rectal wall through the anus.

Peer-review

The authors reported their retrospective data regarding the Delorme's procedure, which is one of the interesting topics.

REFERENCES

1 **Laubert T**, Bader FG, Kleemann M, Esnaashari H, Bouchard R, Hildebrand P, Schlöricke E, Bruch HP, Roblick UJ. Outcome analysis of elderly patients undergoing laparoscopic resection rectopexy for rectal prolapse. *Int J Colorectal Dis* 2012; **27**: 789-795 [PMID: 22249437 DOI: 10.1007/s00384-011-1395-1]

2 **Uhlig BE**, Sullivan ES. The modified Delorme operation: its place in surgical treatment for massive rectal prolapse. *Dis Colon Rectum* 1979; **22**: 513-521 [PMID: 527442 DOI: 10.1007/BF02586995]

3 Classic articles in colonic and rectal surgery. Edmond Delorme 1847-1929. On the treatment of total prolapse of the rectum by excision of the rectal mucous membranes or recto-colic. *Dis Colon Rectum* 1985; **28**: 544-553 [PMID: 3893950]

4 **Riansuwan W**, Hull TL, Bast J, Hammel JP, Church JM. Comparison of perineal operations with abdominal operations for full-thickness rectal prolapse. *World J Surg* 2010; **34**: 1116-1122 [PMID: 20127331 DOI: 10.1007/s00268-010-0429-0]

5 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]

6 **Senapati A**, Gray RG, Middleton LJ, Harding J, Hills RK, Armitage NC, Buckley L, Northover JM. PROSPER: a randomised comparison of surgical treatments for rectal prolapse. *Colorectal Dis* 2013; **15**: 858-868 [PMID: 23461778 DOI: 10.1111/codi.12177]

7 **Makineni H**, Thejeswi P, Rai BK. Evaluation of Clinical Outcomes after Abdominal Rectopexy and Delorme's Procedure for Rectal Prolapse: A Prospective Study. *J Clin Diagn Res* 2014; **8**: NC04-NC07 [PMID: 24995208 DOI: 10.7860/JCDR/2014/7787.4353]

8 **Schoetz DJ**. Evolving practice patterns in colon and rectal surgery. *J Am Coll Surg* 2006; **203**: 322-327 [PMID: 16931304 DOI: 10.1016/j.jamcollsurg.2006.05.302]

9 **Rothenhoefer S**, Herrle F, Herold A, Joos A, Bussen D, Kieser M, Schiller P, Klose C, Seiler CM, Kienle P, Post S. DeloRes trial: study protocol for a randomized trial comparing two standardized surgical approaches in rectal prolapse - Delorme's procedure versus resection rectopexy. *Trials* 2012; **13**: 155 [PMID: 22931552]

10 **Hotouras A**, Ribas Y, Zakeri S, Bhan C, Wexner SD, Chan CL, Murphy J. A systematic review of the literature on the surgical management of recurrent rectal prolapse. *Colorectal Dis* 2015; **17**: 657-664 [PMID: 25772797 DOI: 10.1111/codi.12946]

11 **Steele SR**, Goetz LH, Minami S, Madoff RD, Mellgren AF, Parker SC. Management of recurrent rectal prolapse: surgical approach influences outcome. *Dis Colon Rectum* 2006; **49**: 440-445 [PMID: 16465585 DOI: 10.1007/s10350-005-0315-2]

12 **Pikarsky AJ**, Joo JS, Wexner SD, Weiss EG, Nogueras JJ, Agachan F, Iroatulam A. Recurrent rectal prolapse: what is the next good option? *Dis Colon Rectum* 2000; **43**: 1273-1276 [PMID: 11005496 DOI: 10.1007/BF02237435]

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ORIGINAL ARTICLE

Observational Study

Three-dimensional endoanal ultrasound for diagnosis of perianal fistulas: Reliable and objective technique

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Author contributions: Garcés-Albir M, García-Botello SA and Espi A contributed to study conception and design; Garcés-Albir M and García-Botello SA contributed to data acquisition, data analysis and interpretation, and writing of article; García-Botello SA is a native English speaker; and all the authors contributed to editing, reviewing and final approval of article.

Institutional review board statement: The study was reviewed and approved by the Hospital Clínico Universitario of Valencia Institutional Review Board.

Informed consent statement: All involved persons (subjects or legally authorized representative) gave their informed consent written prior to study inclusion.

Conflict-of-interest statement: None of the authors has conflict of interest of commercial, personal, political, intellectual, or religious.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at garalma@hotmail.com. Participants gave informed consent for data sharing was not obtained but the presented data are anonymized and no risk of identification.

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Abstract

AIM: To evaluate accuracy of three-dimensional endoanal ultrasound (3D-EAUS) as compared to 2D-EAUS and physical examination (PE) in diagnosis of perianal fistulas and correlate with intraoperative findings.

METHODS: A prospective observational consecutive study was performed with patients included over a two years period. All patients were studied and operated on by the Colorectal Unit surgeons. The inclusion criteria were patients over 18, diagnosed with a criptoglandular perianal fistula. The PE, 2D-EAUS and 3D-EAUS was performed preoperatively by the same colorectal surgeon at the outpatient clinic prior to surgery and the fistula anatomy was defined and they were classified in intersphincteric, high or low transsphincteric, suprasphincteric and extrasphincteric. Special attention was paid to the presence of a secondary tract, the location of the internal opening (IO) and the site of external opening. The results of these different examinations were compared to the intraoperative findings. Data regarding location of the IO, primary tract, secondary tract, and the presence of abscesses or cavities was

analysed.

RESULTS: Seventy patients with a mean age of 47 years (range 21-77), 51 male were included. Low transsphincteric fistulas were the most frequent type found (33, 47.1%) followed by high transsphincteric (24, 34.3%) and intersphincteric fistulas (13, 18.6%). There are no significant differences between the number of IO diagnosed by the different techniques employed and surgery (P > 0.05) and, there is a good concordance between intraoperative findings and the 2D-EAUS (k = 0.67) and 3D-EAUS (k = 0.75) for the diagnosis of the primary tract. The ROC curves for the diagnosis of transsphincteric fistulas show that both ultrasound techniques are adequate for the diagnosis of low transsphincteric fistulas, 3D-EAUS is superior for the diagnosis of high transsphincteric fistulas and PE is weak for the diagnosis of both types.

CONCLUSION: 3D-EAUS shows a higher accuracy than 2D-EAUS for assessing height of primary tract in transsphincteric fistulas. Both techniques show a good concordance with intraoperative finding for diagnosis of primary tracts.

Key words: Tridimensional endoanal ultrasound; High transsphincteric fistula; Perianal fistula; Intersphinteric fistula; Dimensional endoanal ultrasound

Core tip: The authors think that this paper provides new information regarding the diagnosis of perianal fistulas with three-dimensional endoanal ultrasound when compared with the results obtained from two-dimensional endoanal ultrasound, physical examination, and examination under anesthesia. This allows us to validate the technique.

Garcés-Albir M, García-Botello SA, Espi A, Pla-Martí V, Martin-Arevalo J, Moro-Valdezate D, Ortega J. Three-dimensional endoanal ultrasound for diagnosis of perianal fistulas: Reliable and objective technique. *World J Gastrointest Surg* 2016; 8(7): 513-520 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i7/513.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i7.513

INTRODUCTION

Management of perianal fistulas continues to be a challenge for the surgeon. The correct classification of the fistulas and their relationship with the anal sphincters is fundamental in choosing the adequate treatment.

Magnetic Resonance Imaging (MRI) and endoanal ultrasound (EAUS) have become the most valuable tools for diagnosing anal pathology. Two dimensional EAUS (2D-EAUS) affords sufficient information to be able to make adequate decisions in the management of these patients[1-4]. It does not however measure volumes of the elements of the anal canal, and gives less information regarding the anatomic structures involved[5-7]. These limitations have been overcome with the introduction of three dimensional EAUS (3D-EAUS).

For many authors, the characteristics of 3D-EAUS (easy access, cost and accuracy) have made it the first choice for the diagnosis of perianal fistulas. To date, examination under anesthesia has been considered the gold standard. There are some groups that now believe MRI is better as it can diagnose fistulas and secondary tracts which are not seen during surgery[8], though there are no studies as yet which investigate the value of 3D-EAUS for this purpose.

The objective of this study was to evaluate the diagnostic accuracy of 3D-EAUS *vs* 2D-EAUS *vs* physical examination (PE) for the diagnosis of perianal fistulas and correlate the results with the intraoperative findings.

MATERIALS AND METHODS

A prospective observational consecutive study was performed with patients included over a two year period. All patients were studied and operated on by surgeon from the Colorectal Unit, Hospital Clínico Universitario, Valencia. The study protocol was approved by the hospital ethics committee and all patients signed an informed consent form.

The inclusion criteria were patients 18 years and over, diagnosed with a cryptoglandular perianal fistula. The exclusion criteria were patients operated in other centres, patients with chronic inflammatory bowel disease, suprasphincteric or extrasphincteric fistulas, and patients who were already receiving nonsurgical treatment which could affect the results such as plugs, biological glues or stem cell therapy, *etc*.

Study protocol

History and PE: A meticulous history was taken during the first consultation. PE performed in the prone jackknife position included palpation of the perianal region and a digital rectal exam. The fistula anatomy was defined and they were classified as intersphincteric, high or low transsphincteric, suprasphincteric and extrasphincteric. Special attention was paid to the presence of a secondary tract, the location of the internal opening (IO) and the site of the external opening (EO).

EAUS: All ultrasounds were performed by the same surgeon with over 10 years' experience in EAUS using the B and K Medical Systems Pro Focus 2202® scanner and B-K 2050 probe (B-K Medical, Herlev, Denmark).

Ultrasound evaluation was carried out at a frequency of 10 MHz initially in 2D and followed by 3D using 0.2 mm slices throughout the length of the anal canal and producing 300 sequential images that were automatically reconstructed as a cube, which could be worked on later.

This automated reconstruction of the images reduces human error as the ultrasound probe does not need to be moved throughout the examination and can be subsequently saved allowing post examination analysis of the 3D-EAUS scan in coronal, sagittal or axial planes as deemed necessary.

All patients were examined in the prone jack-knife position. The ultrasound was systematically performed from the upper to the lower third of the anal canal. When examining the inferior third of the anal canal it is important to keep the buttocks separated because the subcutaneous tissue can be confused with images of the external anal sphincter (EAS) and therefore overestimate the length of the anal canal and of the EAS. When the EO was open the examination was repeated after instilling 10% hydrogen peroxide solution through a cannula.

2D-EAUS: The IO was classified with or without the instillation of hydrogen peroxide according to the criteria proposed by Cho D-Y[9], distance from the anal margin and radial location. The primary fistulous tract was classified as: (1) Not seen; (2) Intersphincteric: Crosses the intersphincteric space without crossing the EAS; (3) Low transsphincteric: Crosses both sphincters or the EAS in the lower two thirds of the anal canal; (4) High transsphincteric: Crosses both sphincters in the upper third of the anal canal; (5) Suprasphincteric: Crosses the intersphincteric space and courses above the upper border of the puborectalis muscle; and (6) Extrasphincteric: Lies external to the sphincteric apparatus.

Other data obtained with this technique were the presence of secondary tracts (hypoechoic tracts which join the primary tract at some point) and the presence of cavities and perianal abscesses.

3D-EAUS: Sagittal, oblique, transverse and coronal images can be obtained and recorded in video format to be reviewed later if necessary. The location and distance of the IO from the anal margin are recorded together with possible secondary tracts and abscesses, confirming or improving the information obtained from the 2D-EAUS.

Once the examination is finalized, the images can be recovered and reviewed, taking meticulous measurements. There are a series of endosonography images that can lead to error in the measurements if the examination is not performed by someone experienced in the field. The separation of the EAS from the puborectalis muscle can be seen on sagittal section as a hypoechoic line, which when combined with the transverse axial image, perfectly defines the proximal limit of the EAS. The proximal limit of the internal anal sphincter (IAS) is defined as the anorrectal junction and quantitative measurements are taken in mm. The following measurements were taken in all patients: Total length of the anal canal, length of the puborectalis muscle, total length of the EAS, total length of the IAS, length of the IAS and EAS involved by the fistula and percentage of sphincter involved by the fistula with respect to the total sphincter length.

According to the measurements obtained, the fistulas were classified by 3D-EAUS as: (1) Unidentified; (2) Intersphincteric: Crosses the intersphincteric space without crossing the EAS; (3) Low transsphincteric: Involves less than 66% of the EAS; (4) High transsphincteric: Involves over 66% of the EAS; (5) Suprasphincteric: Crosses the intersphincteric space and courses above the upper border of the puborectalis muscle; and (6) Extrasphincteric: lies external to the sphincteric apparatus.

Surgery: All patients were operated in the prone jack-knife position with locoregional anesthesia. Surgery is started with a PE under anesthesia using a Hill Ferguson retractor and the EO is probed up to the IO. The presence of secondary tracts and other pathology, which could modify the surgery, is ruled out. If the IO is not seen, 10% hydrogen peroxide is instilled through the EO. At this point, data regarding the site, type, and distance from the anal marginal are taken. The type of surgery to be performed is then chosen.

Statistical analysis

Data from the PE, 2D-EAUS and 3D-EAUS are compared with data from the examination under anesthesia considered the gold standard. The concordance rate and Kappa coefficient (degree of non-random agreement between different measurements of the same variable) are calculated. The Kappa coefficient varies between -1 and 1, considering: k = -1, agreement due to chance; k < 0.2, poor agreement; k = 0.2-0.4, low; k = 0.4-0.6, moderate; k = 0.6-0.8, good; k = 0.8-1, very good. Furthermore, the sensitivity, specificity and predictive values were calculated for each test. The chi-square test was used to compare differences between percentages. The ROC curves (curves for the receiver operating characteristics) have been determined for the diagnosis of transsphincteric fistulas by PE, 2D-EAUS and 3D-EAUS. The ideal diagnostic test has sensitivity and specificity equal to 1 (upper left corner of the curve) and will be poorer the closer it is to the diagonal (area under the curve = 0.50). Therefore, the minimum requirement for a diagnostic method would be an area under the curve greater than 0.50.

In all cases a value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS version 19.0 for Windows (SPSS, Chicago, IL, United States).

RESULTS

Seventy patients with a diagnosis of perianal fistula of criptoglandular origin were eventually included (Figure 1). The most frequent type were low transsphincteric fistulas (33, 47.1%), followed by high transsphincteric

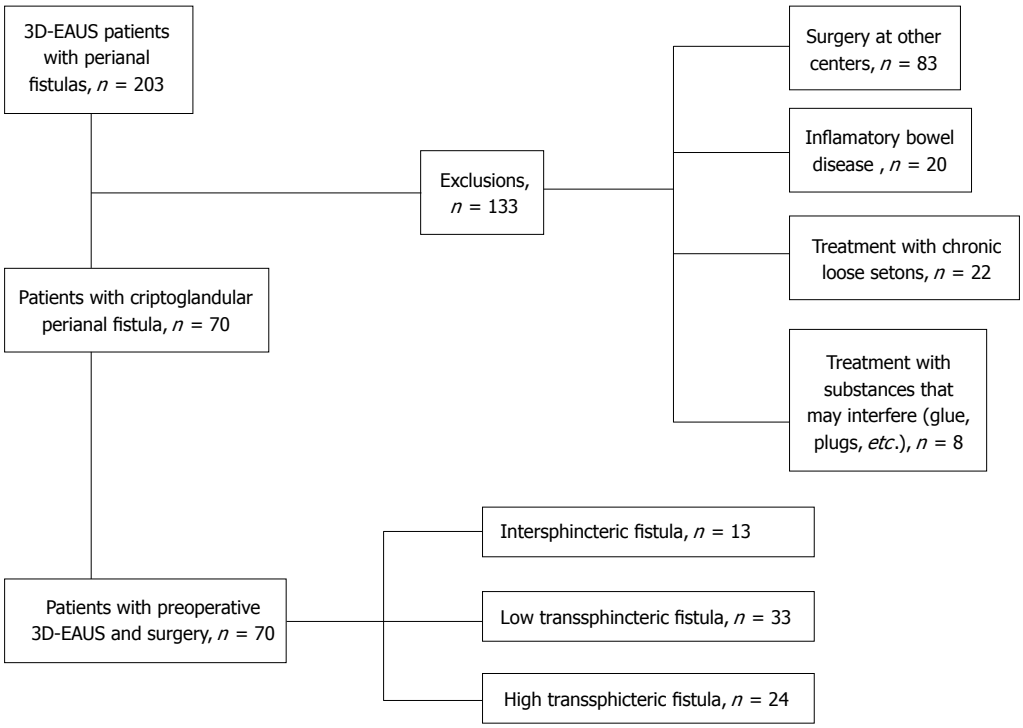

Figure 1 Patient distribution. 3D-EAUS: Three-dimensional endoanal ultrasound.

Table 1 Gynecological history and past perianal surgery

	n = 70 (*n* females = 19)	%
Females with vaginal deliveries	9	47.3
Episiotomy	4	21.0
Hysterectomy	2	10.5
Perianal abscesses drained	42	60.0
Seton	22	31.4
Fistulotomy	6	8.6
Fistulectomy	3	4.3
LIS	7	10.0
Hemorroidectomy	3	4.3
Rectal mucosal advancement flap	3	4.3

LIS: Lateral internal sphincterotomy.

Table 2 Results of fistula evaluation in 70 patients *n* (%)

	PE	2D-EAUS	3D-EAUS	Surgery
IO identified	3 (75.7)	67 (95.7)	67 (95.7)	67 (95.7)
Primary tract				
Intersphincteric	19 (27.1)	14 (20)	10 (14.3)	13 (18.6)
Transsphincteric				
Low	22 (31.4)	25 (35.7)	34 (48.6)	33 (47.1)
High	19 (27.1)	30 (42.9)	25 (35.7)	24 (34.3)
Unclassified	10 (14.3)	1 (1.4)	1 (1.4)	0 (0)
Secondary tract	6 (8.6)	15 (21.4)	16 (22.9)	11 (15.7)
Adjacent abscesses	12 (17.1)	17 (24.3)	19 (27.1)	8 (11.4)

2D-EAUS: Two dimensional endoanal ultrasound; 3D-EAUS: Three dimensional endoanal ultrasound; IO: Internal opening; PE: Physical examination.

fistulas (24, 34.3%) and finally intersphincteric fistulas (13, 18.6%). Gynaecological history and past perianal surgeries can be seen in Table 1. Median duration of symptoms at first consultation was 12 mo (range 1-120).

Correlation with intraoperative findings

Findings for PE, 2D-EAUS, 3D-EAUS and surgery are in Table 2.

Internal opening: Sixty-seven IOs were found in 70 patients intraoperative. The majority of IO were found by digital rectal examination (*n* = 53; 75.7%). Both 2D-EAUS and 3D-EAUS diagnosed 67 IO in 70 patients (95.7%). Both examinations failed to find the IO in 3 patients despite the instillation of hydrogen peroxide. Two of the patients not diagnosed by EAUS do not coincide with those not found during surgery. There are no significant differences between the number of IO diagnosed between the different techniques employed and surgery ($P > 0.05$) (Table 3).

Primary fistula tract

Thirteen intersphincteric fistulas, 33 low transsphincteric and 24 high transsphincteric fistulas were diagnosed intraoperatively. PE could not classify 10 patients due to pain, or because the tract could not be palpated during the examination. Thirty-seven patients were correctly diagnosed (52.9%). 55 (78.6%) and 58 (82.8%) were diagnosed by 2D-EAUS and 3D-EAUS respectively as shown in Table 3. One patient could not be classified by 2D-EAUS or 3D-EAUS due to the difficulty in differentiating the fistulous tract from fibrosis secondary to prior anal surgeries. There is a good concordance between intraoperative and ultrasound diagnosis

Table 3 Concordance grade and k coefficient (k) between intraoperative findings and the different diagnostic techniques used

	PE		2D-EAUS		3D-EAUS	
	Concordance	k	Concordance	k	Concordance	k
IO identified	51/70 (72.8%)	[1]	68/70 (97.1%)	[1]	68/70 (97.1%)	[1]
Primary tract	37/70 (52.9%)	0.33	55/70 (78.6%)	0.67	58/70 (82.8%)	0.75
Secondary tract	61/70 (87.1%)	0.44	64/70 (91.4%)	0.66	65/70 (92.8%)	0.60
Adjacent abscesses	58/70 (82.8%)	0.30	61/70 (87.1%)	0.57	60/70 (85.7%)	0.54

[1]$P > 0.05$. k < 0: No agreement; k = 0: Concordance due to chance; k = 0-0.19: Insignificant; k = 0.2-0.39: Low; k = 0.4-0.59: Moderate; k = 0.6-0.79: good; k = 0.8-0.1: Very good. 2D-EAUS: Two dimensional endoanal ultrasound; 3D-EAUS: Three dimensional endoanal ultrasound; IO: Internal opening; PE: Physical examination.

Table 4 Efficacy parameters in relation to surgery for the different diagnostic techniques: Sensitivity, specificity, positive predictive value and negative predictive value

		S	SP	PPV	NPV
IO identified (%)	PE	76	33	96	6
	2D-EAUS	98	66	98	66
	3D-EAUS	98	66	98	66
Primary tract (%)					
Intersphincteric	PE	69	82	47	92
	2D-EAUS	77	93	71	95
	3D-EAUS	22	98	90	93
Transsphincteric					
Low	PE	45	81	68	67
	2D-EAUS	67	92	88	75
	3D-EAUS	85	84	82	86
High	PE	38	87	68	78
	2D-EAUS	64	76	70	70
	3D-EAUS	88	91	84	93
Secondary tract (%)	PE	40	97	67	91
	2D-EAUS	90	90	60	98
	3D-EAUS	90	88	56	98

2D-EAUS: Two-dimensional endoanal ultrasound; 3D-EAUS: Three-dimensional endoanal ultrasound; PE: Physical examination; IO: Internal opening; S: Sensitivity; SP: Specificity; PPV: Positive predictive value; NPV: Negative predictive value.

of primary tract, the highest concordance was with 3D-EAUS (k = 0.67 and k = 0.75, respectively). There is a tendency to overestimate fistula height with 2DEAUS as can be seen by the lower specificity for high transsphincteric fistulas and lower sensitivity for low transsphincteric fistulas shown in Table 4.

Secondary fistulous tracts: One or more secondary fistula tracts were diagnosed by 2D-EAUS and 3D-EAUS in 15 and 16 patients respectively with a good concordance with surgical findings (91.4%, k = 0.66; 92.8%, k = 0.60) (Table 3).

Abscesses and adjacent cavities: 2D-EAUS diagnosed abscesses in 17 (24.3%) patients and 3D-EAUS in 19 (27.1%) patients. 12 cases (17.1%) were diagnosed by PE. 8 patients (11.4%) presented with an abscess at the time of surgery. There was a moderate concordance between EAUS and surgery (k=0.57, k = 0.54, respectively). There was a low concordance between PE and intraoperative findings (k = 0.30) (Table 3).

Table 5 Results of receiver operatives characteristic curves for the diagnosis of transsphinteric fistulas

		Area under curve	95%CI	*P* value
Low	PE	0.608	0.474-0.742	0.120
transsphincteric	2D-EAUS	0.819	0.714-0.924	0.0001
fistula	3D-EAUS	0.829	0.724-0.934	0.0001
High	PE	0.672	0.541-0.803	0.019
transsphincteric	2D-EAUS	0.842	0.745-0.939	0.0001
fistula	3D-EAUS	0.910	0.835-0.985	0.0001

2D-EAUS: Two-dimensional endoanal ultrasound; 3D-EAUS: Three-dimensional endoanal ultrasound; PE: Physical examination.

The sensitivity and specificity (efficacy indexes) of the different examinations with respect to intraoperative findings are shown in Table 4.

ROC curves (Receiver Operating Characteristic) for the diagnosis of transsphincteric fistulas by PE and 2D/3D-EAUS are adequate for the diagnosis of low transsphincteric fistulas. 3D-EAUS is superior for the diagnosis of high transsphincteric fistulas (Figure 2). PE is clearly deficient for the classification of transsphincteric fistulas (Table 5).

DISCUSSION

3D-EAUS is a novel technique for the diagnosis of perianal fistulas and multiple studies such as ours demonstrate its' superiority with respect to 2D-EAUS. 3D-EAUS is a useful tool that gives a more reliable preoperative diagnosis of perianal fistulas with accurate diagnosis of the IO, primary tracts, secondary tracts and adjacent abscesses or cavities. Ratto *et al*[10] published a rate of exact diagnosis with 3D-EAUS of primary and secondary tracts of 98.5% and 96.4% for the IO compared with 89.9%, 83.3% and 87.9% respectively with 2D-EAUS. Santoro *et al*[11,12] in their study in 57 patients confirm that 3D-EAUS improves diagnosis accuracy of the IO when compared to 2D-EAUS (2D-EAUS: 66.7% *vs* 3D-EAUS: 89.5%; *P* = 0.0033). However, both techniques were similar for diagnosis of primary and secondary tracts and abscesses[11,12]. Our study showed a 97.1% concordance for the diagnosis of the IO (for both types of EAUS), 78.6% for primary tracts, 91.4% for secondary tracts and 87.1% for cavities and abscesses with 2D-EAUS as opposed to

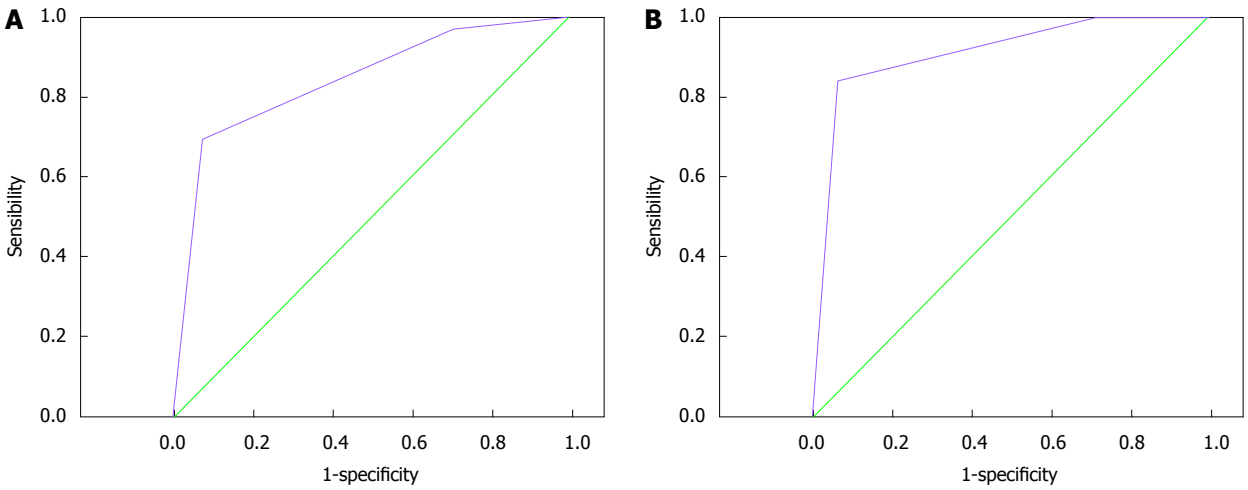

Figure 2 Receiver operating characteristic curves for the diagnosis of high transsphincteric fistulas with two-dimensional endoanal ultrasound (A) (area under curve = 0.842; 95%CI: 0.745-0.939; *P* = 0.0001) and three-dimensional endoanal ultrasound (B) (area under curve = 0.910; 95%CI: 0.835-0.985; *P* = 0.0001).

82.8%, 92.8% and 85.7% respectively when using 3D-EAUS. A preliminary study in 29 patients carried out by our group showed a concordance rate between intraoperative findings (gold standard) and 3D-EAUS of 79% for primary fistula tracts validating the latter as a useful technique in the evaluation of perianal fistulas[13].

There are various classifications for perianal fistulas. As a practical method, various authors have modified the Parks classification[14]. The subdivision of transsphincteric fistulas with regards to the level at which they cross the anal canal tends to be arbitrary dividing these in equal thirds. We propose a new division of transsphincteric fistulas dividing them into low (less than 66% of the total length of the EAS involved) and high (over 66% of the EAS involved). This way we can simplify the classification and guide the indication for surgery.

This study shows a good correlation between 3D-EAUS and surgical findings, with superior results to PE and 2D-EAUS, in particular with regards to high transsphincteric fistulas which are the ones raising more doubts in diagnosis and choice of treatment. According to our results, 2D-EAUS in particular for high transsphincteric fistulas tends to overestimate the amount of anal sphincter involved thus classifying them as higher than they really are, as can be seen by the lower specificity for high transsphincteric fistulas and lower sensitivity for low transsphincteric fistulas. These errors are minimized with 3D-EAUS with a notable improvement in sensitivity and specificity. According to the ROC curves, the best technique for diagnosing high transsphincteric fistulas is 3D-EAUS. Although both types of EAUS are adequate for the diagnosis of low transsphincteric fistulas, 3D-EAUS seems to be slightly superior.

The large variability between examinations have not allowed for the calculation of the IO Kappa coefficient, there were no significant differences between examination techniques and surgical findings with regards to diagnosis of the IO. These results are similar to the study in 21 patients published by Poen *et al*[15]. The three examinations show high sensitivity and specificity when diagnosing the location and distance from the anal margin of the IO.

Even though both types of EAUS have a good concordance 3D-EAUS has shown a higher concordance and accuracy than 2D-EAUS when compared to intraoperative findings (k = 0.75 *vs* k = 0.67). Various studies have shown a very good concordance between 2D and 3D-EAUS and surgery for diagnosis of the primary tract using the instillation of hydrogen peroxide[8,13]. We did not use hydrogen peroxide in all our patients and included patients with a closed EO. This could explain the difference in results.

Similar to the results published by Poen *et al*[15] (k = 0.61), 3D-EAUS shows a good concordance with surgery for the diagnosis of secondary tracts (k = 0.60). The concordance coefficient for 2D-EAUS is slightly higher than 3D-EAUS (k = 0.66 *vs* k = 0.60). In addition, EAUS diagnosed more secondary tracts than surgery. These complex or high fistulous tracts could go unnoticed during surgery. As a result of these findings we should possibly reconsider, as have done other authors, which of these examinations is truly the gold standard for the diagnosis of perianal fistulas. Surgery may not be the best diagnostic tool and we should consider MRI with an endoanal coil or 3D-EAUS[16].

The diagnosis of adjacent abscesses and cavities shows a moderate concordance with surgery (2D-EAUS, k = 0.57; 3D-EAUS, k = 0.54) and insignificant concordance with PE. This is probably due to the fact that these cavities may not be obvious on PE but as patients had to wait sometime between examination and surgery there were probably changes (improvement or deterioration) in these parameters.

There are various studies that defend the routine use of preoperative 2D-EAUS for the diagnosis of both simple and complex perianal fistulas[14,17]. Some

simple perianal fistulas can be diagnosed on PE and we believe a routine EAUS is unnecessary. 3D-EAUS has clearly overtaken 2D-EAUS however, and is more efficient offering more detailed information[10,18]. Due to the common problem that these fistulas represent and the difficulty in obtaining a definitive treatment, there are various groups that as we do, use 3D-EAUS for the preoperative diagnosis of perianal fistulas[19]. Murad-Regadas *et al*[20] published a study in 33 patients confirming that preoperative 3D-EAUS was useful for the diagnosis of anterior transsphincteric fistulas, assisting in choosing the most appropriate treatment and reducing the incontinence rates.

Our work shows the value of 3D-EAUS in predicting the amount of sphincter involved by the fistula in an objective and quantitative manner, and allowing a more accurate classification of the fistula.

Despite the results obtained in this study there were some limitations. These include the low number of patients included even though this was similar or superior to other published studies, the exclusion of suprasphincteric and extrasphincteric fistulas, whose prevalence is very low and where the role of IRM *vs* 3D-EAUS is debatable[7,16]; and that all measurements and scans in this study were performed by the same surgeon. This last point may be beneficial on the one hand as it reduces interobserver variability, but at the same time may offer some bias. We believe it would be more correct to perform the measurements by two independent examiners and then analyse the differences between them.

According to our results we can conclude that 3D-EAUS is more accurate than 2D-EAUS for estimating the height of the primary tract in transsphincteric fistulas. Both 2D and 3D-EAUS techniques show a good concordance with examination under anesthesia for the diagnosis of primary tracts with slightly superior results for 3D-EAUS. Therefore, we agree with other authors that EAUS is a fundamental tool in the evaluation of perianal fistulas allowing for a better classification. 3D-EAUS provides new advantages with respect to 2D-EAUS and is a superior technique allowing for objective and quantitative, and not only subjective, information.

COMMENTS

Background

Perianal fistulas are a common problem in the general population and affect around 10 per 100000 population per year. The relationship between fistulous tract, the sphincters and adequate management is still a challenge today. Imaging techniques play an important role in diagnosis. Various authors including us prefer endoanal ultrasound (EAUS). It is cheaper, easy to use with training, fast, non-invasive and can be used in the operating room if necessary.

Research frontiers

Controversy has been raised over the last few years over which technique [magnetic resonance imaging (MRI), ultrasound or examination under anesthesia] is the gold standard for diagnosis of perianal fistulas. The choice between EAUS and MRI mainly depends on their availability. MRI may seem to offer better results for the diagnosis of perianal fistulas but is outweighed by its' expense and lower availability. In addition, three-dimensional (3D)-EAUS has considerably improved when compared with MRI.

Innovations and breakthroughs

This study compares the results of PE, 2D-EAUS and 3D-EAUS with examination under anesthesia for perianal fistulas providing concordance data for the different techniques. This allows the authors to determine which technique is best in each case, the need to use them as diagnostic tools and for providing optimal management of perianal fistulas.

Applications

The results of this study suggest 3D-EAUS is superior to 2D-EAUS for the diagnosis of high transsphincteric fistulas and could now be considered the gold standard for diagnosis of this pathology. EAUS is a fundamental tool for the evaluation of perianal fistulas offers an accurate classification and therefore betters treatment.

Terminology

Perianal fistulas are a chronic phase of a suppurated anal disease. The currently available imaging techniques for classifying anal fistulas are: Fistulography (no longer used), MRI and EAUS. EAUS can be 2D EAUS (distance, area and volume measurements cannot be taken, with poorer imaging of spatial relations and loss of relevant information) or 3D-EAUS (offers a view of all planes and distances, angles, areas and volumes can be accurately measured).

Peer-review

The paper offers an interesting comparison of the diagnostic yield of 2D-EAUS *vs* 3D-EAUS for perianal fistulas. The gold standard in the present study are intraoperative findings, although other groups think that MRI can demonstrate perianal fistulas missed by the surgeon.

REFERENCES

1 **Voyvodic F**, Rieger NA, Skinner S, Schloithe AC, Saccone GT, Sage MR, Wattchow DA. Endosonographic imaging of anal sphincter injury: does the size of the tear correlate with the degree of dysfunction? *Dis Colon Rectum* 2003; **46**: 735-741 [PMID: 12794574 DOI: 10.1007/s10350-004-6650-x]

2 **Law PJ**, Talbot RW, Bartram CI, Northover JM. Anal endosonography in the evaluation of perianal sepsis and fistula in ano. *Br J Surg* 1989; **76**: 752-755 [PMID: 2670055 DOI: 10.1002/bjs.1800760737]

3 **Cataldo PA**, Senagore A, Luchtefeld MA. Intrarectal ultrasound in the evaluation of perirectal abscesses. *Dis Colon Rectum* 1993; **36**: 554-558 [PMID: 8500372 DOI: 10.1007/BF02049861]

4 **Lindsey I**, Humphreys MM, George BD, Mortensen NJ. The role of anal ultrasound in the management of anal fistulas. *Colorectal Dis* 2002; **4**: 118-122 [PMID: 12780634 DOI: 10.1046/j.1463-1318.2002.00295.x]

5 **Bartram CI**, Frundiger A. Handbook of anal endosonography. Petersfield, Wrightson Biomedical, 1997: 15-20

6 **Hildebrandt U**, Feifel G, Schwarz HP, Scherr O. Endorectal ultrasound: instrumentation and clinical aspects. *Int J Colorectal Dis* 1986; **1**: 203-207 [PMID: 3298489 DOI: 10.1007/BF01648337]

7 **Law PJ**, Bartram CI. Anal endosonography: technique and normal anatomy. *Gastrointest Radiol* 1989; **14**: 349-353 [PMID: 2680741 DOI: 10.1007/BF01889235]

8 **West RL**, Dwarkasing S, Felt-Bersma RJ, Schouten WR, Hop WC, Hussain SM, Kuipers EJ. Hydrogen peroxide-enhanced three-dimensional endoanal ultrasonography and endoanal magnetic resonance imaging in evaluating perianal fistulas: agreement and patient preference. *Eur J Gastroenterol Hepatol* 2004; **16**: 1319-1324 [PMID: 15618839 DOI: 10.1097/00042737-200412000-00014]

9 **Cho DY**. Endosonographic criteria for an internal opening of fistula-in-ano. *Dis Colon Rectum* 1999; **42**: 515-518 [PMID: 10215054 DOI: 10.1007/BF02234179]

10 **Ratto C**, Grillo E, Parello A, Costamagna G, Doglietto GB.

Endoanal ultrasound-guided surgery for anal fistula. *Endoscopy* 2005; **37**: 722-728 [PMID: 16032490 DOI: 10.1055/s-2005-870155]

11 **Santoro GA**, Fortling B. The advantages of volume rendering in three-dimensional endosonography of the anorectum. *Dis Colon Rectum* 2007; **50**: 359-368 [PMID: 17237912 DOI: 10.1007/s10350-006-0767-z]

12 **Santoro GA**, Ratto C, Di Falco G. Three-dimensional reconstructions improve the accuracy of endoanal ultrasonography in the identification of internal openings of anal fistulas. *Colorectal Dis* 2004; **6** Suppl 2: 214

13 **Garcés Albir M**, García Botello S, Esclápez Valero P, Sanahuja Santafé A, Espí Macías A, Flor Lorente B, García-Granero E. [Evaluation of three-dimensional endoanal endosonography of perianal fistulas and correlation with surgical findings]. *Cir Esp* 2010; **87**: 299-305 [PMID: 20392442 DOI: 10.1016/j.ciresp.2010.02.006]

14 **Navarro-Luna A**, García-Domingo MI, Rius-Macías J, Marco-Molina C. Ultrasound study of anal fistulas with hydrogen peroxide enhancement. *Dis Colon Rectum* 2004; **47**: 108-114 [PMID: 14719157 DOI: 10.1007/s10350-003-0015-8]

15 **Poen AC**, Felt-Bersma RJ, Eijsbouts QA, Cuesta MA, Meuwissen SG. Hydrogen peroxide-enhanced transanal ultrasound in the assessment of fistula-in-ano. *Dis Colon Rectum* 1998; **41**: 1147-1152 [PMID: 9749499 DOI: 10.1007/BF02239437]

16 **West RL**, Zimmerman DD, Dwarkasing S, Hussain SM, Hop WC, Schouten WR, Kuipers EJ, Felt-Bersma RJ. Prospective comparison of hydrogen peroxide-enhanced three-dimensional endoanal ultrasonography and endoanal magnetic resonance imaging of perianal fistulas. *Dis Colon Rectum* 2003; **46**: 1407-1415 [PMID: 14530683 DOI: 10.1007/s10350-004-6758-z]

17 **Pascual Migueláñez I**, García-Olmo D, Martínez-Puente MC, Pascual Montero JA. Is routine endoanal ultrasound useful in anal fistulas? *Rev Esp Enferm Dig* 2005; **97**: 323-327 [PMID: 16004524]

18 **Kruskal JB**, Kane RA, Morrin MM. Peroxide-enhanced anal endosonography: technique, image interpretation, and clinical applications. *Radiographics* 2001; **21** Spec No: S173-S189 [PMID: 11598256 DOI: 10.1148/radiographics.21.suppl_1.g01oc13s173]

19 **Brillantino A**, Iacobellis F, Di Sarno G, D'Aniello F, Izzo D, Paladino F, De Palma M, Castriconi M, Grassi R, Di Martino N, Renzi A. Role of tridimensional endoanal ultrasound (3D-EAUS) in the preoperative assessment of perianal sepsis. *Int J Colorectal Dis* 2015; **30**: 535-542 [PMID: 25728829 DOI: 10.1007/s00384-015-2167-0]

20 **Murad-Regadas SM**, Regadas FS, Rodrigues LV, Holanda Ede C, Barreto RG, Oliveira L. The role of 3-dimensional anorectal ultrasonography in the assessment of anterior transsphincteric fistula. *Dis Colon Rectum* 2010; **53**: 1035-1040 [PMID: 20551756 DOI: 10.1007/DCR.0b013e3181dce163]

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SYSTEMATIC REVIEWS

Benefits of post-operative oral protein supplementation in gastrointestinal surgery patients: A systematic review of clinical trials

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Author contributions: All authors contributed equally to the work; Crickmer M and Dunne CP conceived the study; Crickmer M, Dunne CP and Coffey JC designed the search; Crickmer M, O' Regan A and Dunne SS performed the searches and analysed the data; all authors contributed to drafting of the manuscript.

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Abstract

AIM: To evaluate published trials examining oral post-operative protein supplementation in patients having undergone gastrointestinal surgery and assessment of reported results.

METHODS: Database searches (MEDLINE, BIOSIS, EMBASE, Cochrane Trials, Cinahl, and CAB), searches of reference lists of relevant papers, and expert referral were used to identify prospective randomized controlled clinical trials. The following terms were used to locate articles: "oral" or "enteral" and "postoperative care" or "post-surgical" and "proteins" or "milk proteins" or "dietary proteins" or "dietary supplements" or "nutritional supplements". In databases that allowed added limitations, results were limited to clinical trials that studied humans, and publications between 1990 and 2014. Quality of collated studies was evaluated using a qualitative assessment tool and the collective results interpreted.

RESULTS: Searches identified 629 papers of which, following review, 7 were deemed eligible for qualitative evaluation. Protein supplementation does not appear to affect mortality but does reduce weight loss, and improve nutritional status. Reduction in grip strength deterioration was observed in a majority of studies, and approximately half of the studies described reduced complication rates. No changes in duration of hospital stay or plasma protein levels were reported. There is evidence to suggest that protein supplementation should be routinely provided post-operatively to this population. However, despite comprehensive searches, clinical trials that varied only the amount of protein provided *via* oral nutritional supplements (discrete from other nutritional

components) were not found. At present, there is some evidence to support routinely prescribed oral nutritional supplements that contain protein for gastrointestinal surgery patients in the immediate post-operative stage.

CONCLUSION: The optimal level of protein supplementation required to maximise recovery in gastrointestinal surgery patients is effectively unknown, and may warrant further study.

Key words: Protein supplementation; Gastrointestinal surgery; Clinical trial; Oral supplementation; Systematic review

Core tip: Malnutrition in hospitalized patients can negatively impact recovery; protein and energy deficiencies have been documented in gastrointestinal surgery patients and trials have demonstrated benefits of perioperative nutritional strategies, although post-operative oral nutritional supplementation have been studied to a lesser extent. The outcome of our work is that clinical trials that varied only the protein provided *via* oral supplements were not found. There is evidence to support oral protein supplements for gastrointestinal surgery patients immediately post-operatively. But the optimal level of protein supplementation required to maximise recovery in gastrointestinal surgery patients is effectively unknown, and may warrant further study.

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INTRODUCTION

Malnutrition has been associated with increased incidence of complications such as sepsis, pneumonia, wound infections, clotting disorders, and wound dehiscence[1,2]. Patients undergoing major gastrointestinal surgery can suffer periods of undernourishment, not only as a consequence of their presenting illness, but also due to reduced food intake and the resulting catabolic state that prevails in the post-operative period. In this population, malnutrition has been found to increase post-operative morbidity and mortality rates as well as the duration and subsequent cost of hospital stay[3,4]. These despite multimodal nutritional regimens, include pre-operative carbohydrate loading.

In this context, nutritional supplementation has been suggested as a routine post-operative procedure for gastrointestinal surgery patients given the putative negative nitrogen balance. Indeed, intervention in the form of post-operative protein supplementation (in the context of allowable free-fluids or light diet by mouth) has remained of interest as an effective way to improve patient recovery despite an apparent paucity of trials adequately addressing the optimum, or even appropriate, quantity of proteins or peptides. As the physiological nitrogen balance is affected by both energy and protein consumption, knowledge of the levels of each that best enable avoidance of catabolic loss after gastrointestinal surgery could benefit patient outcomes[5].

Therefore, in this review, clinical trials of oral nutritional supplements providing increased protein levels relative to controls, administered to human patients recovering from gastrointestinal surgery, were systematically assessed with respect to clinical efficacy and cost-effectiveness.

MATERIALS AND METHODS

Search methods

The following terms were used to locate articles: "oral" or "enteral" and "postoperative care" or "post-surgical" and "proteins" or "milk proteins" or "dietary proteins" or "dietary supplements" or "nutritional supplements". In databases that allowed added limitations, results were limited to clinical trials that studied humans, and publications between 1990 and 2014. Despite these limits, multiple non-clinical trial results, non-human trials, and irrelevant studies appeared and were excluded. The search was intentionally broad as more specific searches for gastrointestinal surgery associated keywords and MeSH terms resulted in numerous missed relevant papers. Databases searched included: MEDLINE, Biosis, EMBASE, Cochrane Trials, Cinahl, and CAB. Other means of identifying records included searching reference lists of relevant papers.

Inclusion and exclusion criteria

Randomized controlled clinical trials examining protein-based oral dietary supplementation post-operatively in human gastrointestinal surgery patients were selected. Studies were excluded if: Involved immunonutrition; related to supplementation with incomplete proteins; did not specify the amount of protein supplemented; supplemented patients pre-operatively only; not strictly oral nutrition; or not published in English.

Outcomes measured

Primary outcomes included the effect of supplementation on post-operative complications, length of hospital stay, nutritional status, and weight loss. Secondary outcomes included the effect on plasma proteins, quality of life, function, and cost of care.

Data collection and analysis

Trials that met the inclusion criteria were independently assessed for eligibility by the authors (Crickmer M, O' Regan A, Dunne CP) and discrepancies were resolved

Table 1 Quality assessment tool (adapted from[6])

Items and scores
Was the assigned treatment adequately concealed prior to allocation?
2 = method did not allow disclosure of assignment
1 = small but possible chance of disclosure of assignment or states random but no description
0 = quasi-randomized
Were the outcomes of participants who withdrew described and included in the analysis (intention to treat)?
2 = intention-to-treat analysis based on all cases randomized possible or carried out
1 = states number and reasons for withdrawal but intention-to-treat analysis not possible
0 = not mentioned or not possible
Were the outcome assessors blinded to treatment status?
2 = action taken to blind assessors, or outcomes such that bias is unlikely
1 = small or moderate chance of unblinding of assessors
0 = not mentioned
Were the treatment and control group comparable at entry?
2 = good comparability of groups
1 = confounding small
0 = large potential for confounding, or not discussed
Were care programs, other than the trial options, identical?
2 = care programs clearly identical
1 = clear but unimportant differences
0 = not mentioned or clear and important differences in care programs
Were the inclusion and exclusion criteria clearly defined?
2 = clearly defined
1 = inadequately defined
0 = not defined
Were the interventions clearly defined (including estimates of nutritional value)?
2 = clearly defined interventions are applied with a standardized protocol
1 = clearly defined interventions are applied but the application protocol is not standardized
0 = intervention and/or application protocol are poorly or not defined
Were the participants blind to assignment status following allocation?
2 = effective action taken to blind participants
1 = small or moderate chance of unblinding participants
0 = not possible, or not mentioned (unless double-blind), or possible but not done
Were the treatment providers blind to assignment status?
2 = effective action taken to blind treatment providers
1 = small or moderate chance of unblinding of treatment providers
0 = not possible, or not mentioned (unless double-blind), or possible but not done
Was the overall duration of surveillance clinically appropriate?
2 = optimal (six months or more)
1 = adequate (one up to six months)
0 = not defined, or not adequate

by discussion. Papers were read independently by the authors and themes were identified. Risk of bias was assessed by determining allocation concealment for participants, the staff and assessors. The effect of treatment was assessed relative to clinical importance and statistical significance, using *P* values of $\leqslant$ 0.05 as the cut-off point. The evaluation of the trials was guided thematically with the qualitative tool, modified from a previous Cochrane Systematic Review[6], described in Tables 1 and 2. The characteristics of each study were tabulated and are shown in Table 3.

Where studies included both pre-and post-operative supplementation interventions, only the post-operative components are considered in this review. The numbers of trial participants per study were adjusted to reflect this.

RESULTS

Results of the search

Following PRISMA guidelines[7], seven eligible reports were identified (see Figure 1). Exclusions were as follows: (1) of records found *via* database searching: 358; (2) of records found by other means: 271; (3) of records screened: 629; (4) of records excluded (including removal of duplicates): 587; (5) of full text articles assessed for eligibility: 42; (6) of full text articles excluded: 35; and (7) of studies included in qualitative analysis: 7.

Assessment of studies design

All seven studies[5,8-13] were prospective randomized controlled trials. In most cases, the patients, their carers and the assessors were not blinded. Intention to treat was not included in most studies. The control and intervention groups had similar characteristics in each trial and in all other aspects of treatment, other than the intervention. The interventions undertaken, and inclusion and exclusion criteria, were well defined in all studies. Five of the seven studies[5,8,9,11,13] included outpatient phases that lasted between one and six months. The characteristics of the studies are outlined

Table 2 Outcomes of quality assessment, described for individual trials

	Smedley *et al*[8]	Saluja *et al*[10]	Beattie *et al*[13]	MacFie *et al*[9]	Jensen *et al*[5]	Keele *et al*[11]	Rana *et al*[12]
Was the treatment adequately concealed prior to allocation?	2	0	2	0	0	0	2
Were candidates who withdrew included in analysis?	0	No withdrawals	0	0	0	0	1
Were the assessors blinded?	0	0	0	0	2		0
Were treatment and control groups comparable at entry?	2	2	0 Specific mention of "lack of detail on patients at entry"	2	1 Specific mention of error "in the randomisation process"	2	2
Were care programmes otherwise identical?	2	2	2	2	2	2	2
Were the inclusion and exclusion criteria clearly defined?	2	2	2	2	2	2	2
Were the interventions clearly defined?	2	2	2	1	1	2	2
Were the participants blind to assignment after allocation?	0	0	0	0	0	0	0
Were the treatment providers blinded to allocation status?	0	0	0	0	0	0	0
Was duration of surveillance appropriate?	1	1	2	2	1	1	0

in Table 3.

Sample sizes and patient population

Sample sizes ranged from 40 to 101. A total of 529 patients were involved, 262 of whom had an intervention. Participants were post-operative gastrointestinal surgery patients scheduled for acute or elective surgery. Nutritional status pre-operatively was variable, with some studies focused on malnourished patients[10,13]. Patient age ranged from 18 to greater than 75, and all studies included both genders.

Interventions

All treatment group (TG) patients received post-operative nutritional supplementation in addition to their normal ward diet, while control groups (CGs) consumed only normal ward diet. In most cases, patients were encouraged to drink 200-400 mL of the supplement per day. Supplements comprised between 0.0078 g/mL and 0.06 g/mL of protein, with the most frequent value being 0.05 g/mL. They also provided between 0.6 kcal/mL and 1.5 kcal/mL of energy, with the most common inclusion being 1.5 kcal/mL. All studies, except Jensen[5], began supplementation as soon as allowed by the surgical team, typically beginning one to six days post-operatively. Some studies focused on post-operative feeding only, while studies by Smedley *et al*[8] and MacFie *et al*[9] examined both pre-operative and post-operative feeding. Only the post-operative component of those studies is considered in this review and the numbers of trial participants has been adjusted to reflect this.

Themes

Assessment was according to the following eight themes:

Overall nutritional intake: Four of the studies quantified the difference in protein intake between treatment and CGs. Specifically, Saluja *et al*[10] found that protein intake was significantly higher ($P < 0.01$) in the group given supplementation in addition to ward diet. The TG consumed an average of 55.71 ± 11.63 g of protein per day during the study period, while the CG consumed 39.48 ± 11.14 g of protein per day ($P < 0.01$). These increases in protein consumption were accompanied by significant increases in the amount of carbohydrate consumed ($P < 0.01$). Jensen *et al*[5] calculated that the TG consumed 22% more protein than the CG and 16% more energy. It is noteworthy that supplementation in that trial started after discharge at about day 10, and was paired with dietetic advice, while in the previous trial by Saluja *et al*[10], supplementation began the first day following surgery. Keele *et al*[11] also found that the TG showed statistically significant increases in protein and energy consumption on study days one to four. No difference in protein intake was seen in the second phase of their trial, which examined intake for 4 mo following discharge. The inpatient results (improved overall nutritional intake) found by Rana *et al*[12] are similar to those found by Keele *et al*[11].

Weight: Four of five studies that measured this factor[5,8,11,12] found reduced weight loss in normonourished patients receiving supplementation. Keele *et al*[11] found decreased loss both at day 3 of the trial and at discharge ($P < 0.001$). Rana *et al*[12] found that when patients started supplements as soon as they were allowed free fluids after surgery, they maintained their weight whereas by day 3, there was significant weight loss in the CG ($P < 0.05$). Statistically significant reduction in weight loss was also found by Smedley

Table 3 Summary details of eligible trials

Ref.	Method	Participants	Intervention	Outcomes	Conclusions/Notes
Smedley *et al*[8]	RCT	Undergoing elective moderate-major lower GI surgery n = 89; 39 patients were controls in the pre-op phase and in the TG in phase 2 making them the treatment group for this analysis. Fifty patients were controls throughout making them the control group	Included multiple groups with patients receiving pre and post-operative supplementation. This review focused on the group that received no supplements pre- and post-op, as well as the group that received no supplement pre-op and supplements post-operation (CG = Group 4, TG = Group 3) Supplementation began when patients allowed light diet or free fluids post-operation. Fortisip, nutricia used as supplement: 0.05 g/mL protein, 1.5 kcal/mL energy TG asked to drink as they desired in addition to meals	Complications: Fewer minor complications in TG (P < 0.05) Length of stay: No difference Weight loss: Significant reduction in patients given ONS before and after surgery and in patients given postoperative ONS only Quality of life: No difference (Short Form 36, EuroQol instruments were used) Cost: Reduced by GBP£300 (15%) per patient, however not statistically significant Post-surgery oral nutritional supplements were of benefit independently of nutritional status	The patients in this study had a baseline of good nutritional intake
Saluja *et al*[10]	PRCT	n = 60 (30/30) divided into BM, MM and SM using the NRI[26] Age: Between 20-60 yr Elective and emergency abdominal procedures (not just GI) Treatment started from day-1 post-operatively Assessment was done on admission, day 3 and at discharge	0.033 g/mL of protein or 16.66 g/500 mL drink and 500 kcal energy, in addition to ward diet. Ward diet only was provided to control group. Trial started once surgical team allowed fluids or light diet	Adverse events: ONS well tolerated Total protein intake: Increased in TG (P < 0.01) Voluntary protein intake higher though not significant Weight loss: TG = 2.15 kg *vs* CG = 4.6 kg (P < 0.01) Overall weight loss: TG = 5.6%, CG = 6.4% Severely Malnourished Patients: TG = 6.3%, CG = 10% (P < 0.01) No significant change in lymphocyte count Complications: No significant difference Length of stay: Statistically significant reduction in severely malnourished patients. No difference in other categories in length of stay No change in mid arm circumference No change in hand grip strength Treatment group felt better than control group (subjective assessment) No difference in voluntary intake in group consuming supplements	Severely malnourished patients have increased energy requirements and less oral intake, and will therefore lose lean body mass as a substrate for energy Albumin half-life is 20 d - early post-op period is too short to demonstrate a difference due to supplementation

Beattie *et al*[13]	PRCT	Patients had a BMI < 20 or > 5% weight loss between hospital admission and trial inclusion, and other anthropometric criteria. Age: 18-80 *n* = 101, intervention = 52; control = 49	Oral nutritional supplement containing 0.06 g/mL protein, 1.5 kcal/mL energy. Patients encouraged to consume 400 mL/d postoperatively. In practice, patients had between 200 and 400 mL/d in addition to normal meals	Weight loss: CG lost an average maximum of 5.96 kg at 8 wk after admission, while TG lost a maximum of 3.4 kg on average in the first 4 wk and then gained weight ($P < 0.001$) Mean body weight loss = 9.8% in CG and 5.6% in treatment group Triceps skin fold and MAMC were higher in TG than CG ($P < 0.001$) Function: Improved grip strength at 10 wk ($P < 0.001$) Quality of life (UK SF-36): Statistically significant improvement in mental and physical health ($P < 0.001$) Complications: Reduced ($P < 0.05$) No difference in infection rates Length of stay: No difference	Support for nutritional intervention in patients with malnutrition: Post-operative oral nutritional supplementation improved nutritional status, quality of life and morbidity
MacFie *et al*[9]	PRCT	Major GI surgery patients *n* = 52; 27 had intervention of some kind. TG *n* = 27 (post op supplements), CG *n* = 25	Pre and post-operative phases. For this review, only the control group and post-operative supplementation group were looked at Fortisip, Nutricia given - 0.05 g/mL protein and 1.5 kcal energy/mL or an alternative Fortijuice, Nutricia containing 0.025 g/mL protein and 1.25 kcal/mL energy. Patients encouraged to consume 400 mL/d in addition to normal ward diet Supplementation commenced as soon as permitted fluids post-surgery, usually within 24 h CG was provided standard ward diet	Nutritional intake: Increased protein and energy seen (but no benefits could be seen) Morbidity: No difference Mortality: No difference Effect on voluntary food intake: No difference Nutritional status: No difference Functional status: No difference Hospital stay: No difference Weight Loss: No significant difference Serum albumin: No significant difference Psychological Status: No significant differences Return to normal activities at 6 mo: No difference No evidence that increased supplements decreased amount of ward diet eaten	Similar intakes of supplements as previous trials (Rana, Keele) that showed benefit Also concluded: No difference in benefit when looked at the 17 malnourished patients in the study Possible lack of difference due to small study numbers in each group, or in general, early return to eating post-surgery in practice along with dietician support normally at the hospital
Jensen and Hessov[5]	RCT - Supplements given after discharge from colorectal surgery for 4 mo	Elective and acute *n* = 87: 47 in CG and 40 in TG	Control group: Discharged without advice TG: Dietetic advice and a variety of supplements including protein only - aiming for 1.5 g protein/kg per day	Body mass: (50 d after discharge) lean body mass increase seen in TG of 1.3 kg ($P = 0.009$) and in overall body mass 2.0 kg ($P = 0.005$). 110 d after discharge: Total mass difference was +2.7 kg for TG relative to CG ($P = 0.014$), and lean body mass +1.4 kg for TG ($P = 0.029$) No significant difference in fat mass was seen at either stage Serum albumin: No difference was seen at any time	Initially patients in the intervention group gained LBM without fat mass; later there were gains in both types of mass Recommendation: Patients should increase protein intake to 1.5 g/kg per day for 2 mo post-surgery

Keele *et al*[11]	Short and long term (4 mo after discharge) benefits of intervention	*n* = 100 moderate-major elective GI surgery; *n* = 53 in CG and *n* = 47 in TG.	TG was given oral nutritional supplement post-operatively in addition to ward diet, which was given to the control group	Inpatient phase	Phase 1 assessment was at day 3 and discharge
			In-patient and out-patient phases (to 4 mo after discharge)	Nutrient intake: Significant increase in protein and energy intake increase at days 1 and 2 ($P < 0.001$) and 3 (energy $P < 0.01$, protein $P < 0.001$), day 4 ($P < 0.05$) and day 7 - protein only ($P < 0.05$)	Clinically significant benefits with short term supplementation but not long term supplementation
	(There were four groups in this study: C/C had no supplementation before/after surgery; C/S had none before and supplementation after; S/C had supplementation before and none after; S/S had supplementation before and after surgery		Supplement consumption was "ad libitum"	No significant difference in intake of energy or protein from ward diet	Both CG and TG had below requirement levels of protein as in-patients
	For the purposes of the review C/C were taken as CG and C/S were taken as TG)		Supplements - 200 mL cartons of Fortisip with 1.5 kcal and 0.05 g/mL (10 g protein/carton)	Energy intake 1 m after discharge: Significantly higher in TG	By 1 mo, patients in both groups were eating well so supplements had little effect on well-being
				Weight loss: Less in treatment group at day 3 and discharge ($P < 0.001$)	The rapidity of the effects of protein supplementation suggests that its effect is due to a direct action of key nutrients rather than repletion of tissue stores
				Serious complications: Less in treatment group ($P < 0.05$)	
				Handgrip: Significant reduction in CG at days 3 and 7; strength lost at day 3 in treatment group but regained by discharge	
				Subjective fatigue: Increased fatigue in CG at day 3 and discharge ($P < 0.001$), no significant increase in fatigue in TG	
				Complications: More in control group ($P < 0.05$)	
				Giving food did not reduce voluntary food intake	
				Outpatient phase	
				Nutrient Intake: No significant difference in protein intake in the out-patient phase. Significantly higher energy intake was seen ($P < 0.05$) in groups consuming supplements post-discharge compared to controls	
				No benefit was seen with supplementation post-discharge	

Rana *et al*[12]	Short term only: Started on day patients could receive free fluids until discharge	n = 40; 20 control and 20 supplemented	Ad libitum supplementation with oral nutritional sip feed in addition to control diet	Nutritional intake: significantly higher energy intake in the treatment group $P < 0.004$ (as well as the nutritional value of the supplements, more energy was consumed from ward diet by these patients) and protein intake (due solely to supplements)	In the CG there is a significant protein deficit by day 3 which persisted to day 7 (often the day of discharge)
		Major G-I surgery	7.8 g/L unhydrolysed protein. 1.5 kcal/mL energy density. 1.4 L is needed to provide all required nutrient as defined by United Kingdom health board	Significant weight loss in CG but not TG at day 3 and discharge	5-6 d on average elapsed between day of operation and day 1 of study period where diet was allowed. Study period began when surgical team allowed "free-fluids or light diet"
			Controls and given ward diet and allowed snacks	Grip strength difference at day 3 and discharge ($P < 0.03$) in favor of treatment group	Within 3 d of "free fluids/light diet" treatment patients were consuming 70 g protein/d and about 2000 kcal
				No difference in mid-arm circumference/triceps skin folds changes between groups	Observed increased number of calories (not protein) being eaten from ward diet in the treatment group - inference that supplementation helped to maintain appetite
				Serious complications (pneumonia, wound infection) significantly higher in CG	
				No difference in length of stay	
				Complications: Pneumonia and wound infection seen. $P < 0.02$ in favor of treatment group	
				Blood proteins: No difference in serum albumin, retinol binding albumin, prealbumin. Significant difference in retinol binding protein as CG declined while TG levels remained same. $P < 0.05$	
				Hospital stay length: No statistically significant difference	

TG: Treatment group; CG: Control group; RCT: Randomised controlled trial; PRCT: Prospective randomised controlled trial; ONS: Oral nutritional supplement; MAMC: Mid-arm muscle circumference; LBM: Lean body mass; BM: Borderline malnourished; MM: Moderately malnourished; SM: Severely malnourished; NRI: Nutritional risk index.

et al[8] ($P < 0.05$). In the trial by Jensen *et al*[5], supplementation was not started before discharge, typically around 10 d post-operatively, but at both 50 and 110 d after discharge, the intervention group had increased total and lean body mass. No other studies looked specifically at lean body mass. Conversely, however, MacFie *et al*[9] reported no significant difference in weight loss between control and intervention groups overall.

Studies by Saluja *et al*[10] and Beattie *et al*[13] noted reduced weight loss in the malnourished patient population investigated in their studies, but no difference was seen by MacFie *et al*[9] when he isolated the 17 malnourished patients from his study. More specifically, Beattie *et al*[13] found that controls lost an average of 5.96 kg in 8 wk, while intervention patients lost 3.4 kg on average in the first 4 wk and then gained weight ($P < 0.001$). Saluja *et al*[10] quantified the average weight loss in the TG as 2.15 kg compared to 4.6 kg in the CG ($P < 0.01$).

Postoperative complications: None of the studies found a difference in mortality between control and TGs. A wide variety of other complications were looked at including chest and wound infection, sepsis, cardiac arrest, pulmonary embolism, and wound dehiscence. Three of the 6 trials that investigated complications found a reduced number in the TG: Smedley *et al*[8] found reduced minor complications ($P < 0.05$) but no difference in major complications. Both Keele *et al*[11] and Rana *et al*[12] demonstrated significantly fewer serious complications in their short term studies ($P < 0.05$). No difference in post operative complications was found by Saluja *et al*[10] or MacFie *et al*[9]. Saluja *et al*[10] did find a reduction in infectious complications in severely malnourished patients, but numbers were too small for statistical significance. Similarly, Beattie *et al*[13] saw a reduction in complications that was not significant when adjusting for age and sex.

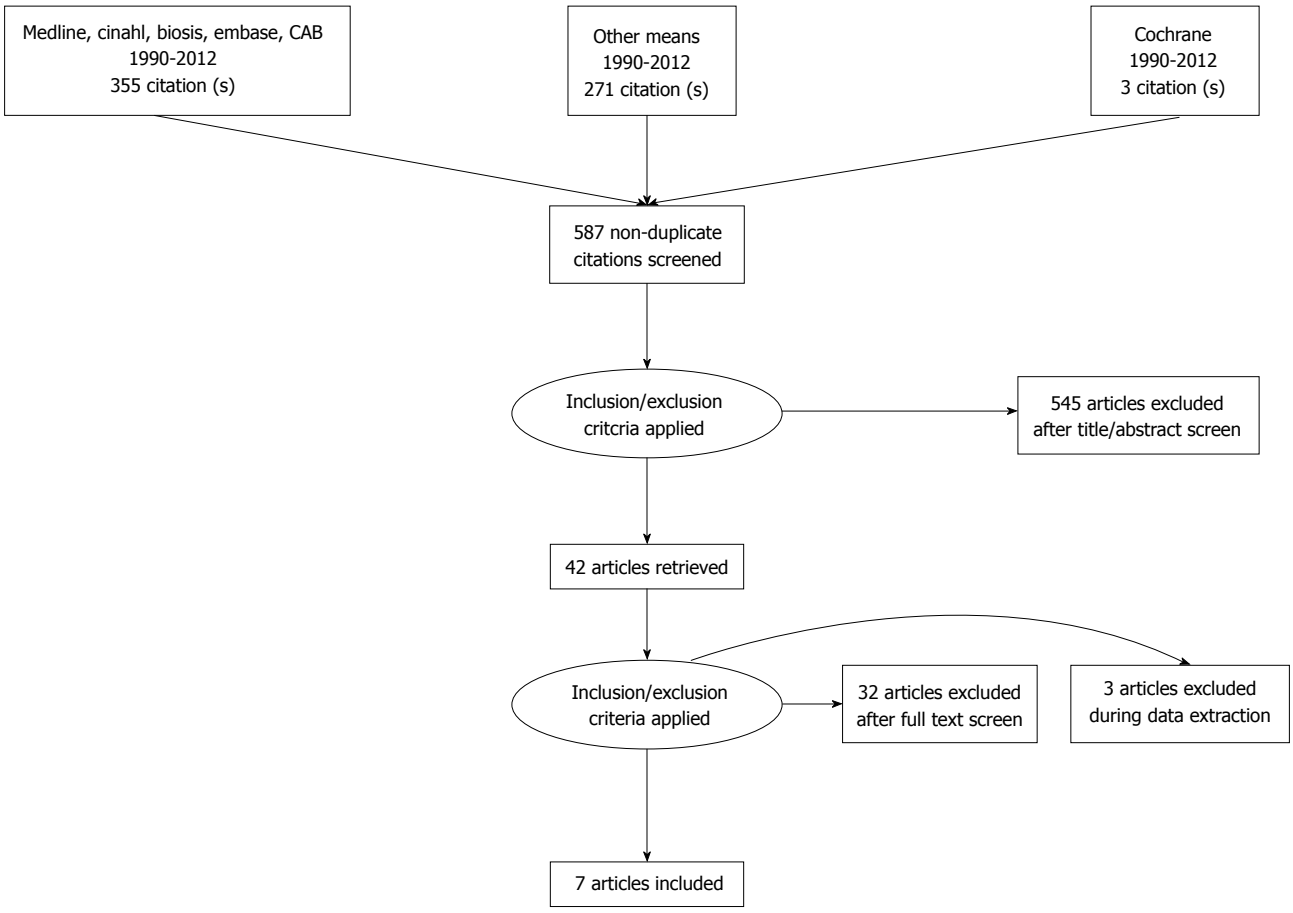

Figure 1 PRISMA guidelines.

Length of stay: The study by Saluja *et al*[10] determined a difference in length of stay between treatment and CGs in severely malnourished patients, but no difference in moderately or borderline malnourished patients. Beattie's study[13], which also looked at malnourished patients, found no difference. The three studies[8,12,13] that evaluated length of stay in normonourished patients found no difference.

Plasma proteins: Four studies investigated plasma proteins levels[5,9,10,12], with albumin the focus of most of these studies. None of these found any significant difference in serum albumin or prealbumin. Rana *et al*[12] found increased retinol binding protein in the TG relative to controls at day three ($P < 0.05$).

Cost: Smedley *et al*[8] found that the use of oral nutritional supplementation, irrespective of when administered, decreased cost by £300 (sterling) per patient amounting to a 15% reduction compared to patients without supplementation. This was not statistically significant. No other study considered cost of care.

Grip strength: Three of five studies that investigated grip strength found reduced loss of grip strength in patients receiving oral nutritional supplements relative to controls. Keele *et al*[11] found that handgrip was maintained in the intervention group and significantly reduced in controls ($P < 0.01$). Rana *et al*[12] found a significant difference at day three and again at discharge ($P < 0.05$). Beattie *et al*[13] found similar results and noted statistical significance in the differences at week 10 ($P < 0.001$). Saluja *et al*[10] and MacFie *et al*[9] detected no difference in hand grip strength after supplementation.

Quality of life and fatigue: Beattie *et al*[13] found increased quality of life in the TG using the short form 36 questionnaire (SF-36)[14] in both mental and physical health ($P < 0.001$). Smedley *et al*[8] used SF-36 and EuroQol instruments to test quality of life and found no difference. Keele *et al*[11] subjectively assessed fatigue and found significant increases in control patients at study day three ($P < 0.001$), while TG increases in fatigue were not significant.

DISCUSSION

Previous reviews have concluded that oral nutritional supplements can have positive effects in terms of recovery of nutritional status post-operatively in conditions such as fractured neck of femur, colorectal surgery, and pancreaticoduodenectomy, among others[15-17]. In these cases, the proposed benefits

could be attributed to protein supplementation (*i.e.*, the amount of orally-consumed protein that confers the greatest benefit) combined with appropriate energy intake[18]. However, what these levels are remain unclear for patients following gastrointestinal surgery. In this review, we attempted to determine this *via* systematic review.

Our searches did not yield a single randomized controlled trial that adequately differentiated the effect of protein supplementation from carbohydrate supplementation. Therefore, analysis of the eligible reports was problematic. Limitations included the fact that protein and energy content in TG supplements were not equivalent in most of the studies. Indeed, only the study by Saluja *et al*[10] described using a fixed amount of supplement for daily consumption, while the remaining studies followed an "ad-libitum" approach. Arguably, the latter approach best mirrors "real-life" clinical scenarios, however it makes discerning the true effect of protein supplementation difficult. Furthermore, the characteristics of the patient cohorts were not equivalent between studies, confounding inter-study comparisons. For example, the study by Saluja *et al*[10] took place in Delhi and included a greater proportion of emergency surgery patients, and patients with tuberculosis, compared with the non-emergent procedures described in the Western European reports. Moreover, inadequate follow up time with control and TGs was common across studies, with some risk of bias associated with lack of blinding of participants, carers and assessors. The power of the studies was often too small, with one author conceding notably that "numbers were too small for meaningful statistical analysis"[13] and intention to treat analysis was not used in any of the studies. Finally, the most recent of the eligible trials found in our searches was published in 2004, arguably reflecting either a shift in interest away from oral intake in favor of enteral and parenteral nutrition in this population or an emphasis placed on ordinary diet without supplement.

Despite these limitations, the authors of six of the seven studies detailed weight loss in patients receiving post-operative nutritional supplements, but to a lesser degree than the loss in control patients[5,8,10-13]. In fact, the data suggest that this effect may be most prominent in patients malnourished initially, with statistically significant reductions in weight loss observed. While one study failed to observe this effect[9], despite similar energy and protein intakes to other trials, the authors proposed that the lack of effect was due to a small sample size. Finally, with respect to weight gain post-operatively, it appears that weight gain commenced sooner and patients appeared to return to their preoperative weight more rapidly where supplementation was provided.

There is no evidence to suggest that nutritional supplementation post-operatively reduces mortality. While more deaths did occur in the CGs of the reported trials, much larger samples would be needed to approach statistical significance. The topic of avoidance of both serious and minor complications is less clear. There is some precedent to suggest that post-operative supplementation decreases complications, as the effect has been documented in patients undergoing hip surgery[15,19,20]. However, across the eligible studies here, the rate of both serious and minor complications was significantly reduced in four of the trials[8,11-13], while no statistically significant difference was observed in two[9,10]. This variation has been addressed somewhat by Beattie *et al*[13] when comparing his results to the study by MacFie *et al*[9] in making reference to discrepancies in defining complications. On a related topic, duration of hospitalization was reduced significantly in severely malnourished patients only[10]. An additional study that supplemented increased amounts of protein and medium chain carbohydrates in enteral feed in gastrointestinal patients post-operatively found a 6-d reduction on average ($P < 0.05$)[21]. However, that study had larger numbers than any of the studies considered in this review, with 229 total and 115 TG patients. It has also been suggested that length of stay is a relatively poor outcome to evaluate as it often depends on patient social circumstances and services available in addition to patient post-operative clinical condition[12].

With respect to malnutrition, and assessment of patient incidence, low albumin has been used as a measurable indicator, but evidence suggests that it is not an effective marker of recent nutritional intake[22]. Approximately 5% of the circulating albumin is replaced daily by the liver and, therefore, any changes in protein intake would not be evident immediately. Further, protein markers in the blood such as prealbumin, albumin and transferrin are impacted by fluid shifts and responses to injury and inflammation which complicate their use in comparisons of patients before and after major abdominal surgery, when tissue injury is present[23]. This may explain why none of the studies in our review that monitored albumin in the early post-operative period found any disparity in albumin levels despite differences in anthropometric indicators of malnutrition (*e.g.*, triceps skin fold, mid upper arm circumference and BMI[23]). Similarly inconsistent results were found regarding quality of life.

Evaluation of quality of life and physiological function were similarly inconsistent. For example, handgrip strength is a marker of function and results were variable across the trials. However, those variances may be explained by the use of dissimilar techniques for measurement, and confounders such as pain and fatigue post-operatively. Interestingly, the TGs in the studies conducted by MacFie *et al*[9] and Saluja *et al*[10] both described increased total body mass retention relative to CGs, but without significant increases in grip strength. Jensen *et al*[5] found that supplementation increased lean body mass particularly, not simply fat mass, so one could hypothesize that a functional measurement

like grip strength would also be improved, but this was not described. Previous work has documented a link between impaired muscle function and nutritionally-related complications[24,25], but this was not consistently reflected across the eligible trials here.

The seven studies reviewed in this paper concurred that there is no difference in mortality seen with protein-inclusive nutritional supplements. There is evidence to suggest that weight reduction, nutritional intake, and nutritional status are improved, and that there may be positive cost of hospitalisation benefits, but evidence as to the effect on complications and grip strength is mixed. At present, there is some evidence to support routinely prescribed oral nutritional supplements that contain protein for gastrointestinal surgery patients in the immediate post-operative stage. However, randomized control trials using well-designed methodology to examine the optimal protein content needed to confer benefit are needed.

COMMENTS

Background

Malnutrition in hospitalized patients can negatively impact recovery; protein and energy deficiencies have been documented in gastrointestinal surgery patients and trials have demonstrated benefits of perioperative nutritional strategies, although post-operative oral nutritional supplementation have been studied to a lesser extent. The proposed benefits may be attributed to protein supplementation (*i.e.*, the amount of orally-consumed protein that confers the greatest benefit) combined with appropriate energy intake. However, what those levels may be remain unclear for gastrointestinal surgery patients.

Research frontiers

The positive impact of pre-operative nutrition has been reviewed previously and meta-analyses have demonstrated positive influence on patient outcome following gastrointestinal surgery. In the postoperative period however, the most pertinent question may be whether patients should be further supplemented. The most recent of the eligible trials found in the searches was published in 2004.

Innovations and breakthroughs

The authors' searches did not yield a single randomized controlled trial that adequately differentiated the effect of protein supplementation from carbohydrate supplementation. With only one exception, the eligible studies reviewed here involved post-operative supplements administered "ad-libitum". Although this may best mirror "real-life" clinical scenarios, it makes discerning the true effect of protein supplementation difficult. Furthermore, the characteristics of the patient cohorts were not equivalent between studies. Despite these limitations, the authors of six of the seven studies detailed weight loss in patients receiving post-operative nutritional supplements, but to a lesser degree than the loss in control patients. There is no evidence to suggest that nutritional supplementation post-operatively reduces mortality and evaluation of quality of life and physiological function were similarly inconsistent.

Applications

An intervention based on oral protein supplementation should be investigated through a double-blind randomized controlled trial.

Terminology

There are no terms used that are uncommon and that would be unfamiliar to readers.

Peer-review

The authors have made a good collation of the data to assess if there are any benefits of post-operative protein nutritional supplementation following gastrointestinal surgery. The manuscript is well written and covers the salient points from the published studies.

REFERENCES

1 **Burden S**, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. *Cochrane Database Syst Rev* 2012; **11**: CD008879 [PMID: 23152265 DOI: 10.1002/14651858.CD008879.pub2]

2 **Hulsewe K**, Von Meyenfeldt M, Soeters P, Payne-James J, Grimble G, Silk, DBA Nutrition support for the surgical patient. In: Payne-James J, Grimble G, Silk DBA, editors. Artificial nutrition support in clinical practice. 2ed. Cambridge University Press, 2001

3 **Dempsey DT**, Mullen JL, Buzby GP. The link between nutritional status and clinical outcome: can nutritional intervention modify it? *Am J Clin Nutr* 1988; **47**: 352-356 [PMID: 3124596]

4 **Giner M**, Laviano A, Meguid MM, Gleason JR. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. *Nutrition* 1996; **12**: 23-29 [PMID: 8838832 DOI: 10.1016/0899-9007(95)00015-1]

5 **Jensen MB**, Hessov I. Dietary supplementation at home improves the regain of lean body mass after surgery. *Nutrition* 1997; **13**: 422-430 [PMID: 9225334 DOI: 10.1016/s0899-9007(97)91280-6]

6 **Parker MJ**, Gurusamy KS, Azegami S. Arthroplasties (with and without bone cement) for proximal femoral fractures in adults. *Cochrane Database Syst Rev* 2010; **(6)**: CD001706 [PMID: 20556753 DOI: 10.1002/14651858.CD001706.pub4]

7 **Swartz MK**. The PRISMA statement: a guideline for systematic reviews and meta-analyses. *J Pediatr Health Care* 2011; **25**: 1-2 [PMID: 21147401 DOI: 10.1016/j.pedhc.2010.09.006]

8 **Smedley F**, Bowling T, James M, Stokes E, Goodger C, O'Connor O, Oldale C, Jones P, Silk D. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *Br J Surg* 2004; **91**: 983-990 [PMID: 15286958 DOI: 10.1002/bjs.4578]

9 **MacFie J**, Woodcock NP, Palmer MD, Walker A, Townsend S, Mitchell CJ. Oral dietary supplements in pre- and postoperative surgical patients: a prospective and randomized clinical trial. *Nutrition* 2000; **16**: 723-728 [PMID: 10978851 DOI: 10.1016/S0899-9007(00)00377-4]

10 **Saluja SS**, Kaur N, Shrivastava UK. Enteral nutrition in surgical patients. *Surg Today* 2002; **32**: 672-678 [PMID: 12181715 DOI: 10.1007/s005950200125]

11 **Keele AM**, Bray MJ, Emery PW, Duncan HD, Silk DB. Two phase randomised controlled clinical trial of postoperative oral dietary supplements in surgical patients. *Gut* 1997; **40**: 393-399 [PMID: 9135531 DOI: 10.1136/gut.40.3.393]

12 **Rana SK**, Bray J, Menzies-Gow N, Jameson J, Payne James JJ, Frost P, Silk DB. Short term benefits of post-operative oral dietary supplements in surgical patients. *Clin Nutr* 1992; **11**: 337-344 [PMID: 16840018 DOI: 10.1016/0261-5614(92)90084-4]

13 **Beattie AH**, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut* 2000; **46**: 813-818 [PMID: 10807893 DOI: 10.1136/gut.46.6.813]

14 **Anderson C**, Laubscher S, Burns R. Validation of the Short Form 36 (SF-36) health survey questionnaire among stroke patients. *Stroke* 1996; **27**: 1812-1816 [PMID: 8841336 DOI: 10.1161/01.STR.27.10.1812]

15 **Bastow MD**, Rawlings J, Allison SP. Undernutrition, hypothermia, and injury in elderly women with fractured femur: an injury response to altered metabolism? *Lancet* 1983; **1**: 143-146 [PMID: 6130196 DOI: 10.1016/S0140-6736(83)92754-X]

16 **Lassen K**, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, von Meyenfeldt MF, Fearon KC, Revhaug A, Norderval S, Ljungqvist O, Lobo DN, Dejong CH. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg* 2009; **144**: 961-969 [PMID: 19841366 DOI: 10.1001/archsurg.2009.170]

17 **Lassen K**, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE,

Schäfer M, Parks RW, Fearon KC, Lobo DN, Demartines N, Braga M, Ljungqvist O, Dejong CH. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr* 2012; **31**: 817-830 [PMID: 23079762 DOI: 10.1016/j.clnu.2012.08.011]

18 **Stroud M**. Protein and the critically ill; do we know what to give? *Proc Nutr Soc* 2007; **66**: 378-383 [PMID: 17637090 DOI: 10.1017/S0029665107005642]

19 **Myint MW**, Wu J, Wong E, Chan SP, To TS, Chau MW, Ting KH, Fung PM, Au KS. Clinical benefits of oral nutritional supplementation for elderly hip fracture patients: a single blind randomised controlled trial. *Age Ageing* 2013; **42**: 39-45 [PMID: 22685164 DOI: 10.1093/ageing/afs078]

20 **Botella-Carretero JI**, Iglesias B, Balsa JA, Arrieta F, Zamarrón I, Vázquez C. Perioperative oral nutritional supplements in normally or mildly undernourished geriatric patients submitted to surgery for hip fracture: a randomized clinical trial. *Clin Nutr* 2010; **29**: 574-579 [PMID: 20199828 DOI: 10.1016/j.clnu.2010.01.012]

21 **Wang X**, Pan L, Zhang P, Liu X, Wu G, Wang Y, Liu Y, Li N, Li J. Enteral nutrition improves clinical outcome and shortens hospital stay after cancer surgery. *J Invest Surg* 2010; **23**: 309-313 [PMID: 21208095 DOI: 10.3109/08941939.2010.519428]

22 **Fuhrman MP**, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. *J Am Diet Assoc* 2004; **104**: 1258-1264 [PMID: 15281044 DOI: 10.1016/j.jada.2004.05.213]

23 **Avenell A**, Handoll HH. Nutritional supplementation for hip fracture aftercare in older people. *Cochrane Database Syst Rev* 2010; **(1)**: CD001880 [PMID: 20091525 DOI: 10.1002/14651858.CD001880.pub5]

24 **Jeejeebhoy KN**. The Practical Nutritional Assessment. In: Buchman A, editor. Clinical Nutrition in Gastrointestinal Disease. Slack Books, 2006

25 **Fritz T**, Höllwarth I, Romaschow M, Schlag P. The predictive role of bioelectrical impedance analysis (BIA) in postoperative complications of cancer patients. *Eur J Surg Oncol* 1990; **16**: 326-331 [PMID: 2379592]

26 Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. *N Engl J Med* 1991; **325**: 525-532 [PMID: 1906987 DOI: 10.1056/NEJM199108223250801]

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Short-term outcomes after laparoscopic colorectal surgery in patients with previous abdominal surgery: A systematic review

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Abstract

AIM: To perform a systematic review focusing on short-term outcomes after colorectal surgery in patients with previous abdominal open surgery (PAOS).

METHODS: A broad literature search was performed with the terms "colorectal", "colectomy", "PAOS", "previous surgery" and "PAOS". Studies were included if their topic was laparoscopic colorectal surgery in patients with PAOS, whether descriptive or comparative. Endpoints of interest were conversion rates, inadvertent enterotomy and morbidity. Analysis of articles was made according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

RESULTS: From a total of 394 citations, 13 full-texts achieved selection criteria to be included in the study. Twelve of them compared patients with and without PAOS. All studies were retrospective and comparative and two were case-matched. The selected studies comprised a total of 5005 patients, 1865 with PAOS. Among the later, only 294 (16%) had history of a midline incision for previous gastrointestinal surgery. Conversion rates were significantly higher in 3 of 12 studies and inadvertent enterotomy during laparoscopy

was more prevalent in 3 of 5 studies that disclosed this event. Morbidity was similar in the majority of studies. A quantitative analysis (meta-analysis) could not be performed due to heterogeneity of the studies.

CONCLUSION: Conversion rates were slightly higher in PAOS groups, although not statistical significant in most studies. History of PAOS did not implicate in higher morbidity rates.

Key words: Previous abdominal surgery; Laparoscopic surgery; Colorectal surgery; Previous abdominal surgery; Laparoscopy

Core tip: So far, there is no substantial evidence in the literature to recommend laparoscopic surgery instead of laparotomy for patients previously submitted to abdominal surgery, concerning short-term benefits, such as conversion rates and morbidity. This review, although without a meta-analysis, brings new light into this matter.

Figueiredo MN, Campos FG, D'Albuquerque LA, Nahas SC, Cecconello I, Panis Y. Short-term outcomes after laparoscopic colorectal surgery in patients with previous abdominal surgery: A systematic review. *World J Gastrointest Surg* 2016; 8(7): 533-540 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i7/533.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i7.533

INTRODUCTION

In colorectal surgery, laparoscopy has been progressively accepted as a good alternative to open surgery since its first reports during the 90's[1,2]. The main benefit attributed to laparoscopy is the associated better short-term outcomes observed in both benign and malignant colorectal diseases[3-6]. Moreover, randomized clinical trials and meta-analysis have suggested that there is no prejudice of oncological outcomes as well[3,7,8].

It is well recognized that the laparoscopic access to treat colorectal diseases is associated with an extended learning curve and has its own limitations. Many patient's, disease's and surgeon's factors may affect operative results, such as previous abdominal open surgery (PAOS), obesity, inflammatory conditions, pregnancy, surgical expertise and others. At the beginning of laparoscopic experience, some of these conditions were even considered contraindications for this approach[9], due to the potential higher risk of intraoperative lesions, during trocar placement or because of visceral adhesions. In practice, these drawbacks were translated into a longer operative time and greater conversion rates. With growing expertise in laparoscopic techniques, surgeons gained confidence to perform more difficult cases and reports of laparoscopic procedures after PAOS have been increasingly published[10-12]. However, there is still a debate concerning the indication of laparoscopic colorectal surgery in patients with PAOS[13,14]. Furthermore, there is no randomized study evaluating the possible benefit of laparoscopic colorectal surgery in the context of PAOS.

Thus, the aim of this study was to perform a systematic review concerning short-term outcomes after laparoscopic colorectal surgery in patients with or without PAOS.

MATERIALS AND METHODS

Incidence of conversion, inadvertent intraoperative intestinal lesions and overall morbidity were our main outcome measures.

Eligibility criteria

Studies were included if they reported results on laparoscopic colorectal surgery in patients with PAOS, whether previously open or laparoscopic, with a special interest if they were comparative. Abstracts only were not included in the systematic review, although they were taken into consideration for discussion.

Search strategy

All authors agreed regarding terms that should be used for online search. The literature search comprised the terms "colorectal", "colectomy", "PAOS", "previous surgery" and "PAOS" in different combinations. Articles were searched if published before August 2014 in the following databases: MEDLINE, EMBASE, Cochrane, Scopus, Scielo and LILACS. Initially the search was not limited by language, but only full texts in English were finally included. References in the selected articles were also searched for additional citations.

Study selection

Titles and abstracts were scanned to identify suitable articles; afterwards abstracts were reviewed to identify studies fulfilling inclusion criteria. Finally, full texts of the interested studies were selected. Two authors performed the study selection and one author was responsible for revision of this selection. There were no conflicts regarding suitability of studies selected or excluded.

Extraction and analysis of data

Two investigators were responsible to extract data from the studies to a previously designed datasheet, interesting outcomes of this study. Another investigator was responsible to review the information and to solve any conflicts. Information collected from the studies was: Overall conversion, inadvertent intraoperative lesions and morbidity. Definition of conversion was not always mentioned in the articles or differed between them. Mostly, conversion referred to unplanned incisions or size of incision in order to complete surgery. We have considered conversion as described in each study, as

Table 1 Definition of conversion in the 13 studies included in the review of patients submitted to laparoscopy with or without previous abdominal surgery

Ref.	Definition of conversion
Hamel *et al*[19]	"any incision unplanned, made sooner than planned or longer than 5 cm"
Kwok *et al*[26]	"abdominal incision exceeded 8 cm; or the incision was extended for any reasons other than division of the bowel and extraction of specimens"
Law *et al*[22]	N/A
Arteaga González *et al*[21]	N/A
Franko *et al*[23]	"change in operative strategy requiring exsufflation of capnoperitoneum and elongation of the surgical incision to allow direct visualization for continued dissection"
Vignali *et al*[14]	"abdominal incision longer than 7 cm or an abdominal incision made earlier or different from that planned at the start of the procedure"
Nozaki *et al*[17]	N/A
Offodile *et al*[25]	"final incision length longer than 7 cm (after skin closure)"
Barleben *et al*[16]	N/A
Fukunaga *et al*[24]	"performance of an unplanned incision"
Maggiori *et al*[18]	"any unplanned incision or a planned incision longer than 6 cm"
Naguib *et al*[20]	N/A
Yamamoto *et al*[13]	"any incision more than 8 cm in length needed to complete or facilitate the procedure that could not be completed" laparoscopically

N/A: Not available.

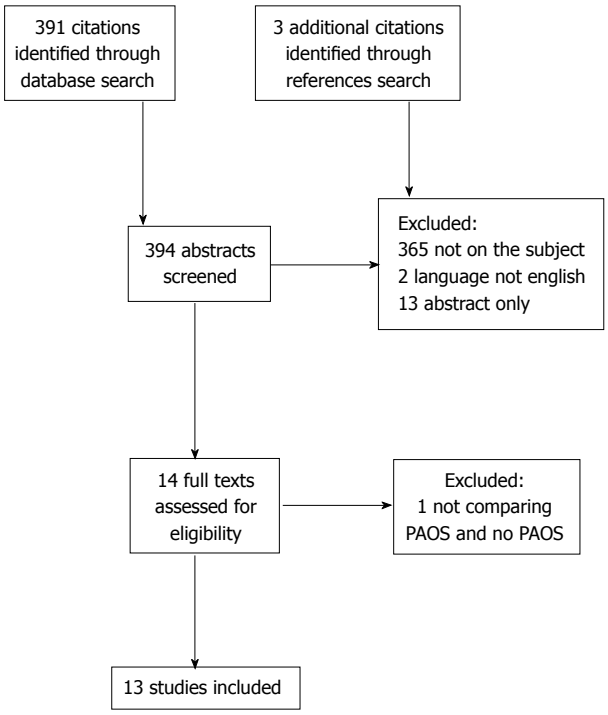

Figure 1 Flow chart: Literature search on MEDLINE, EMBASE, LILACS, Scopus, Scielo, Cochrane.

shown in Table 1.

Analysis of articles was done according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses[15]. Forest plots were done using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

RESULTS

The literature search initially identified 391 articles. Search within references led us to include other 3 articles. Subject of citation did not meet the interest criteria of this study in 365 citations. Two studies were excluded because of language (Chinese and Italian) and 13 had only presented abstracts. Fourteen full-text articles were analysed and 13 studies were included in the present manuscript. One article was excluded because it did not describe nor compared laparoscopy with and without PAOS[13,14,16-26] (Figure 1).

Regarding their characteristics, with one exception, all studies were retrospective and comparative, but only two were case-matched[14,18]. One study was not comparative and only described a group of patients with PAOS[16] (Table 2).

The selected studies comprised a total of 5005 patients, 1865 with PAOS. Four papers included not only open but also laparoscopic previous surgeries, and in most of them some kind of resection was done (*i.e.,* excluding diagnostic laparoscopy and bypasses), excluding one study that included a few patients submitted to a diverting stoma[16]. In two studies[17,23], colorectal surgery included totally laparoscopic and also hand-assisted techniques. Regarding the type of surgical procedures performed, two studies[19,25] described only right colectomies, one included only anterior resections for upper rectum cancer[26], while others included all types of colorectal resections. Three articles included only patients diagnosed with colorectal cancer[17,24,26].

All but three studies[14,18,21] included previous appendectomy. Most previous surgeries described in the studies were appendectomies, gynaecological procedures or cholecystectomies. Of 1865 patients, only 294 (16%) were cited as having had a midline incision for previous gastrointestinal surgeries, while 702 (38%) had a previous appendectomy. Although we cannot separate results of only previous gastrointestinal procedures from gynaecological procedures and cholecystectomies, these 294 cases are the object of our

Table 2 Intraoperative findings of 13 studies in patients submitted to laparoscopy with or without previous abdominal surgery

Ref.	Type of study	No. of patients			Conversion rate (%)			Inadvertent enterotomy (%)		
		Total	PAOS	non PAOS	PAOS	non PAOS	*P*-value	PAOS	non PAOS	*P*-value
Hamel *et al*[19]	Comparative	85	36	49	17	12	0.754	N/A	N/A	N/A
Kwok *et al*[26]	Comparative	91	26	65	15.4	7.7	0.55	N/A	N/A	N/A
Law *et al*[22]	Comparative	295	84	211	17	11	0.181	N/A	N/A	N/A
Arteaga González *et al*[21]	Comparative	86	27	59	26.1	5.1	0.02	0	1.7	NS
Franko *et al*[23]	Comparative	820	347	473	19	11	< 0.001	1.4	0.2	0.04
Vignali *et al*[14]	Case-matched	182	91	91	16.5	8.8	0.18	N/A	N/A	N/A
Nozaki *et al*[17]	Comparative	121	21	100	0	0	N/A	N/A	N/A	N/A
Offodile *et al*[25]	Comparative	414	171	243	17	15	0.42	N/A	N/A	N/A
Barleben *et al*[16]	Observational; not comparative	55	55	0	14.5	N/A	N/A	N/A	N/A	N/A
Fukunaga *et al*[24]	Comparative	607	192	415	5.2	2.6	0.108	2.6	0	0.001
Maggiori *et al*[18]	Case-matched	367	167	200	22	13	0.017	N/A	N/A	N/A
Naguib *et al*[20]	Comparative	181	68	113	13.2	10.6	0.6	2.9	0	0.14
Yamamoto *et al*[13]	Comparative	1701	580	1121	12.4	10.2	0.16	0.9	0.1	0.037
Total		5005	1865	3140						

NS: Not significant; N/A: Not available; PAOS: Previous abdominal surgery.

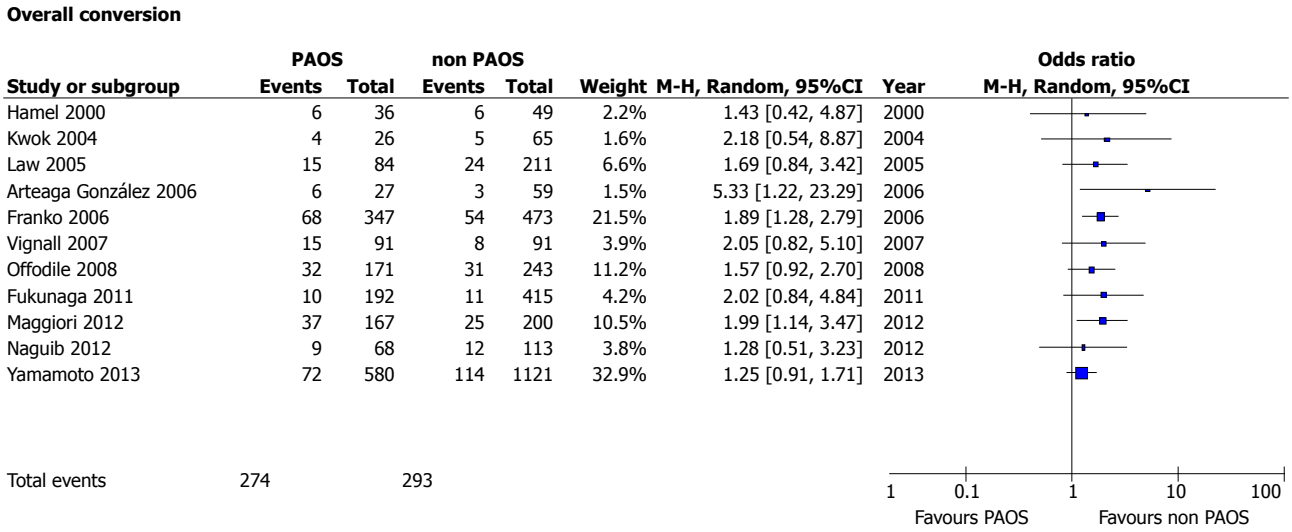

Figure 2 Forest plot showing comparison between studies regarding overall conversion.

interest in this paper.

All studies were retrospective and with great heterogeneity, so a quantitative analysis (mata-analysis) was not carried out because it would not be of value. Nonetheless, a forest plot was made in order to provide an idea of trend in the results of this review, in case data could be adequately extracted.

Conversion

Overall conversion rates were described in all 12 studies (Table 2). These rates were higher in all of the studies but only 3 of studies showed statistical significance[18,21,23] (Figure 2). There were no conversions in one of the studies[17].

Intraoperative inadvertent enterotomy

In 3 of 5 studies, rates of intraoperative intestinal lesions (Figure 3) were higher in the PAOS groups (not necessarily leading to conversion)[13,23,24], while in two studies they were similar[20,21]. The other 8 papers did not describe such data (Table 2).

Postoperative morbidity

In the 9 studies that reported postoperative complication rates, similar rates were reported between patients with and without PAOS (Table 3). In 3 other studies the *P* value comparing overall morbidity rates was not available, but numbers for independent complications were summed in order to perform odds ratio analysis (Figure 4).

DISCUSSION

To date, very few studies have been devoted to evaluate the impact of PAOS on the short-term results after laparoscopic colorectal surgery. The present literature review with more than 5000 patients (including 1800 that had PAOS and 264 with previous gastrointestinal

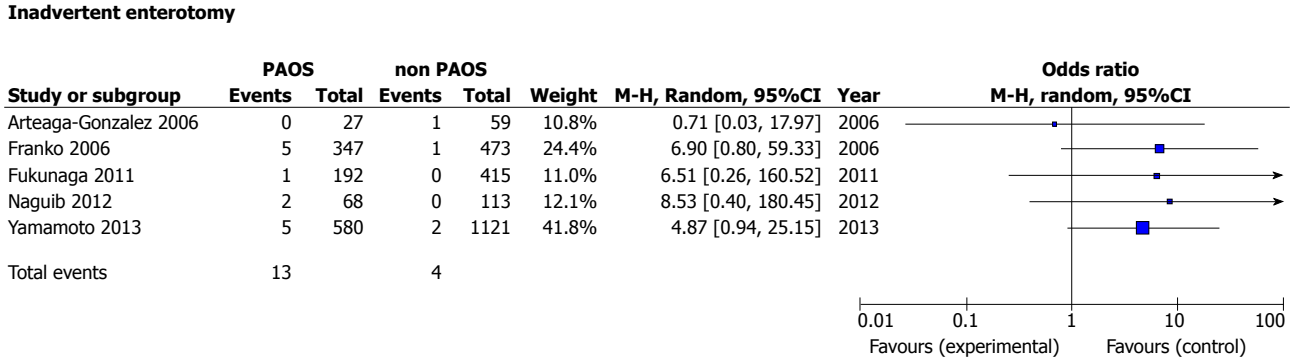

Figure 3 Forest plot showing comparison between studies regarding inadvertent enterotomy.

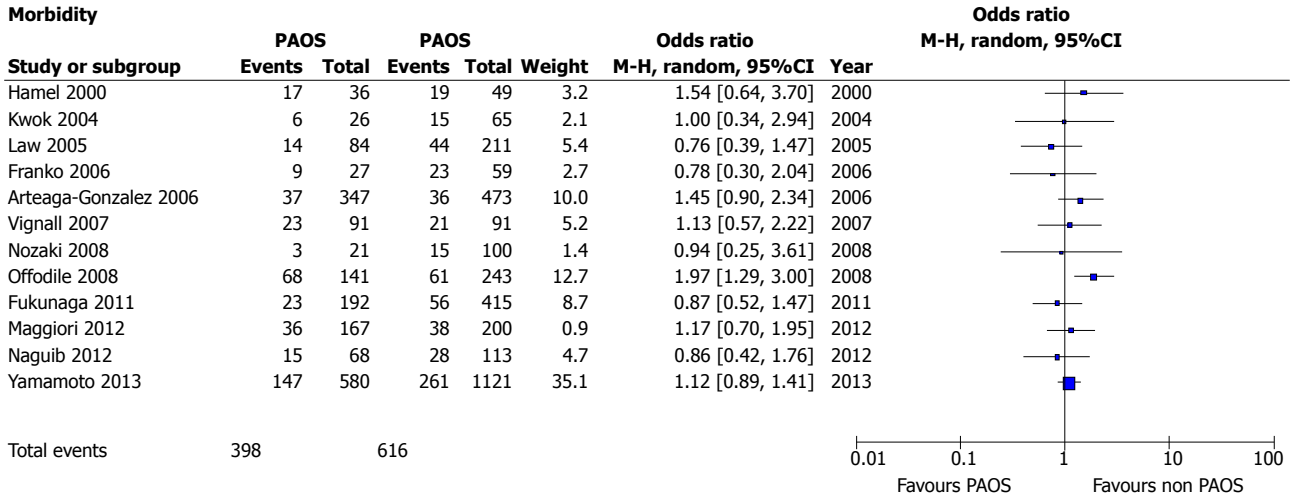

Figure 4 Forest plot showing comparison between studies regarding morbidity.

Table 3 Postoperative findings of 13 studies in patients submitted to laparoscopy with or without previous abdominal surgery

Ref.	No. of patients			Morbidity (%)		
	Total	PAOS	non PAOS	PAOS	non PAOS	*P*-value
Hamel *et al*[19]	85	36	49	47	37	0.18
Kwok *et al*[26]	91	26	65	23	23	0.79
Law *et al*[22]	295	84	211	16	20	0.516
Arteaga González *et al*[21]	86	27	59	39	38	NS
Franko *et al*[23]	820	347	473	N/A	N/A	N/A
Vignali *et al*[14]	182	91	91	25.3	23.1	0.86
Nozaki *et al*[17]	121	21	100	14	15	0.94
Offodile *et al*[25]	414	171	243	N/A	N/A	N/A
Barleben *et al*[16]	55	55	0	N/A	N/A	N/A
Fukunaga *et al*[24]	607	192	415	15.6	14.5	0.767
Maggiori *et al*[18]	367	167	200	22	19	0.543
Naguib *et al*[20]	181	68	113	N/A	N/A	N/A
Yamamoto *et al*[13]	1701	580	1121	25.3	23.3	0.345

NS: Not significant; N/A: Not available; PAOS: Previous abdominal surgery.

resection by midline incision) suggests that PAOS has probably little impact on postoperative morbidity after laparoscopic colorectal surgery.

It is important to state that previous surgery away from the site of the current surgery might not interfere in short-term outcomes, for ex. previous gynaecological surgery in a patient that is going to be submitted to a transverse colon resection should not present a problem regarding technical aspects and subsequent results.

Although conversion rates were higher in few studies (mainly because of adhesion), and the risk of inadvertent enterotomy was also slightly increased, overall postoperative morbidity was similar with or without PAOS. According to the literature, conversion

from laparoscopic to open surgery does not seem to influence directly in post-operative morbidity[27]. In our study, although 3 studies reported higher conversion rates in the PAOS groups, morbidity was similar in both groups.

Due to the heterogeneity of the studies, it was not possible to perform a meta-analysis with qualitative results. This heterogeneity refers not only to statistical methods or study design, but also to different types of surgery (previous and actual) and diseases, as well as experience of the surgeon, which makes it hard to compare as equal.

In a pragmatic approach, laparoscopy should not be contraindicated in patients with PAOS and this is common sense for most surgeons, though it is not well established by current medical literature so far. Although surgeon and patient must be aware of the higher risk of conversion and possible accidental enterotomy, because of all the possible benefits previously demonstrated after laparoscopic colorectal surgery, laparoscopy might be attempted in most of the patients.

Short-term benefits of laparoscopic colorectal resection are clearly demonstrated by several randomized studies, including faster recovery, lower pain, earlier feeding and shorter return of normal intestinal function and shorter hospital stay[6,28-30]. However, it remains controversial if patients still profit from laparoscopic advantages in cases of PAOS. There is no doubt that intra-abdominal adherences may substantially impair intra and postoperative outcomes, mainly due to difficulties when performing adhesiolysis and the risks of visceral perforations. In fact, abdominal adhesions following laparotomy have been described in up to 70% to 90% of patients[31,32], and this may reflect in a longer operative time, mainly due to adhesiolysis, even in open surgery[33], and may lead, also in open surgery, to a higher risk of small bowel lesion in up to 20%[34].

Conversion rates in laparoscopic colorectal surgery range between 5% and 23%[4,35-40]. Although some studies did not find PAOS as a risk factor for higher conversion rates[36,39,41,42], it is believed that PAOS has the potential to increase these rates. In our opinion and practice, we believe that a systematic laparoscopic approach in colorectal surgery for patients with PAOS should be done, except for those with wound dehiscence for which repair is indicated.

Our literature review about laparoscopic surgery in patients with PAOS is in accordance with our strategy: Overall postoperative morbidity was similar whether there was PAOS or not. However, it must be noticed that conversion rates are probably slightly higher in cases of PAOS (demonstrated in only 3/12 studies) mainly because of adhesions, as suggested in 5/6 studies.

We are aware that inflammatory cases (Inflammatory Bowel Disease and diverticulitis) may sometimes present as an even bigger challenge than colorectal cancer and that a learning curve is fundamental for a surgeon to achieve advanced laparoscopic skills and overcome technical difficulties. Therefore, surgeons without significant experience in laparoscopy should carefully select PAOS cases. However, with growing experience in laparoscopic surgery, we consider that adhesion is no more a contraindication to laparoscopic surgery. Even if several minutes might be necessary in the beginning of the procedure to perform adhesiolysis, we consider that avoiding an unnecessary laparotomy may bring several advantages. First, it avoids a traumatic aggression on a previous healed abdominal incision, with the risk of long-term hernia; second, it allows keeping all the short-term advantages of laparoscopy.

In our systematic review, risk of inadvertent enterotomy seems higher with than without PAOS, but this aspect was in fact evaluated in only 5 of 12 studies, and demonstrated in only 3 of those 5 studies.

The main limitation of our review is the heterogeneity of the studies and the absence of prospective studies. For these reasons, it does not allow us to perform quantitative analysis, pooling the results together. Among the studies excluded from our review for being abstracts only, we could also perceive a trend suggesting that conversion rates in patients with PAOS is not higher than that in non PAOS groups[43-47]. In one abstract referring to risk factors for conversion during laparoscopy in colorectal surgery, PAOS was not identified as one[48]. Furthermore, in the context of Crohn's disease, where redo surgery is frequent, two teams have demonstrated that performing a redosurgery by laparoscopy is feasible without increased morbidity rate[43,49], even though short-term benefits might not be the same as in first-time laparoscopies for IBD.

In conclusion, this review suggests that laparoscopic surgery in patients with PAOS is feasible and it is not associated with higher morbidity rates. Although the potential risks of conversion (due to adherences) and inadvertent enterotomies must not be forgotten, we consider that they are not enough to contraindicate laparoscopy in these patients.

COMMENTS

Background

Laparoscopy became the standard technique in many gastrointestinal procedures. But still there is controversy when it comes to perform colorectal surgery in patients that were operated on by a previous laparotomy, since there are no definite studies in this matter. Adhesions and consequent conversion might pose a problem as well as possible higher morbidity rates derived from those. Several articles have compared patients with and without previous abdominal open surgery, but most have a small number of patients, making it harder to make definite assumptions.

Research frontiers

If the authors could consider only patients with previous gastrointestinal resections through midline incision they might bring an even better light in this subject of laparoscopy in case of previous abdominal surgery.

Innovations and breakthroughs

A systematic review concerning a theme that has not been so far elucidated by the current literature, to try to stimulate the debate and since a controlled study with such design is not probable, they might have to take the best evidence

from uncontrolled studies.

Applications

Surgeons might use a systematic revision as an extra support to the belief that previous surgery is no longer a contraindication for laparoscopy in colorectal surgery.

Peer-review

This manuscript is a satisfactorily written systemic review on this problematic subject.

REFERENCES

1 **Jacobs M**, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc* 1991; **1**: 144-150 [PMID: 1688289]

2 **Redwine DB**, Sharpe DR. Laparoscopic segmental resection of the sigmoid colon for endometriosis. *J Laparoendosc Surg* 1991; **1**: 217-220 [PMID: 1834272]

3 **Lacy AM**, García-Valdecasas JC, Delgado S, Castells A, Taurá P, Piqué JM, Visa J. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet* 2002; **359**: 2224-2229 [PMID: 12103285 DOI: 10.1016/S0140-6736(02)09290-5]

4 **Campos FG**, Valarini R. Evolution of laparoscopic colorectal surgery in Brazil: results of 4744 patients from the national registry. *Surg Laparosc Endosc Percutan Tech* 2009; **19**: 249-254 [PMID: 19542856 DOI: 10.1097/SLE.0b013e3181a1193b]

5 **Alves A**, Panis Y, Slim K, Heyd B, Kwiatkowski F, Mantion G. French multicentre prospective observational study of laparoscopic versus open colectomy for sigmoid diverticular disease. *Br J Surg* 2005; **92**: 1520-1525 [PMID: 16231279 DOI: 10.1002/bjs.5148]

6 **Schwenk W**, Haase O, Neudecker J, Müller JM. Short term benefits for laparoscopic colorectal resection. *Cochrane Database Syst Rev* 2005; **(3)**: CD003145 [PMID: 16034888 DOI: 10.1002/14651858.CD003145.pub2]

7 **Fleshman JW**, Nelson H, Peters WR, Kim HC, Larach S, Boorse RR, Ambroze W, Leggett P, Bleday R, Stryker S, Christenson B, Wexner S, Senagore A, Rattner D, Sutton J, Fine AP. Early results of laparoscopic surgery for colorectal cancer. Retrospective analysis of 372 patients treated by Clinical Outcomes of Surgical Therapy (COST) Study Group. *Dis Colon Rectum* 1996; **39**: S53-S58 [PMID: 8831547]

8 **Jayne DG**, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ. Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. *Br J Surg* 2010; **97**: 1638-1645 [PMID: 20629110 DOI: 10.1002/bjs.7160]

9 **Curet MJ**. Special problems in laparoscopic surgery. Previous abdominal surgery, obesity, and pregnancy. *Surg Clin North Am* 2000; **80**: 1093-1110 [PMID: 10987026]

10 **Schirmer BD**, Dix J, Schmieg RE, Aguilar M, Urch S. The impact of previous abdominal surgery on outcome following laparoscopic cholecystectomy. *Surg Endosc* 1995; **9**: 1085-1089 [PMID: 8553208]

11 **Yu SC**, Chen SC, Wang SM, Wei TC. Is previous abdominal surgery a contraindication to laparoscopic cholecystectomy? *J Laparoendosc Surg* 1994; **4**: 31-35 [PMID: 8173109]

12 **Miller K**, Hölbling N, Hutter J, Junger W, Moritz E, Speil T. Laparoscopic cholecystectomy for patients who have had previous abdominal surgery. *Surg Endosc* 1993; **7**: 400-403 [PMID: 8211616]

13 **Yamamoto M**, Okuda J, Tanaka K, Kondo K, Asai K, Kayano H, Masubuchi S, Uchiyama K. Effect of previous abdominal surgery on outcomes following laparoscopic colorectal surgery. *Dis Colon Rectum* 2013; **56**: 336-342 [PMID: 23392148 DOI: 10.1097/DCR.0b013e31827ba103]

14 **Vignali A**, Di Palo S, De Nardi P, Radaelli G, Orsenigo E, Staudacher C. Impact of previous abdominal surgery on the outcome of laparoscopic colectomy: a case-matched control study. *Tech Coloproctol* 2007; **11**: 241-246 [PMID: 17676267 DOI: 10.1007/s10151-007-0358-6]

15 **Moher D**, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535 [PMID: 19622551]

16 **Barleben A**, Gandhi D, Nguyen XM, Che F, Nguyen NT, Mills S, Stamos MJ. Is laparoscopic colon surgery appropriate in patients who have had previous abdominal surgery? *Am Surg* 2009; **75**: 1015-1019 [PMID: 19886156]

17 **Nozaki I**, Kubo Y, Kurita A, Ohta K, Aogi K, Tanada M, Takashima S. Laparoscopic colectomy for colorectal cancer patients with previous abdominal surgery. *Hepatogastroenterology* 2008; **55**: 943-946 [PMID: 18705303]

18 **Maggiori L**, Cook MC, Bretagnol F, Ferron M, Alves A, Panis Y. Prior abdominal open surgery does not impair outcomes of laparoscopic colorectal surgery: a case-control study in 367 patients. *Colorectal Dis* 2013; **15**: 236-243 [PMID: 22738132 DOI: 10.1111/j.1463-1318.2012.03150.x]

19 **Hamel CT**, Pikarsky AJ, Weiss E, Nogueras J, Wexner SD. Do prior abdominal operations alter the outcome of laparoscopically assisted right hemicolectomy? *Surg Endosc* 2000; **14**: 853-857 [PMID: 11000368]

20 **Naguib N**, Saklani A, Shah P, Mekhail P, Alsheikh M, AbdelDayem M, Masoud AG. Short-term outcomes of laparoscopic colorectal resection in patients with previous abdominal operations. *J Laparoendosc Adv Surg Tech A* 2012; **22**: 468-471 [PMID: 22568543 DOI: 10.1089/lap.2011.0383]

21 **Arteaga González I**, Martín Malagón A, López-Tomassetti Fernández EM, Arranz Durán J, Díaz Luis H, Carrillo Pallares A. Impact of previous abdominal surgery on colorectal laparoscopy results: a comparative clinical study. *Surg Laparosc Endosc Percutan Tech* 2006; **16**: 8-11 [PMID: 16552371 DOI: 10.1097/01.sle.0000202188.57537.07]

22 **Law WL**, Lee YM, Chu KW. Previous abdominal operations do not affect the outcomes of laparoscopic colorectal surgery. *Surg Endosc* 2005; **19**: 326-330 [PMID: 15624064 DOI: 10.1007/s00464-004-8114-8]

23 **Franko J**, O'Connell BG, Mehall JR, Harper SG, Nejman JH, Zebley DM, Fassler SA. The influence of prior abdominal operations on conversion and complication rates in laparoscopic colorectal surgery. *JSLS* 2006; **10**: 169-175 [PMID: 16882414]

24 **Fukunaga Y**, Kameyama M, Kawasaki M, Takemura M, Fujiwara Y. Laparoscopic colorectal surgery in patients with prior abdominal surgery. *Dig Surg* 2011; **28**: 22-28 [PMID: 21293128 DOI: 10.1159/000321955]

25 **Offodile AC**, Lee SW, Yoo J, Whelan RL, Moradi D, Baxter R, Arnell TD, Nasar A, Sonoda T, Milsom JW, Feingold DL. Does prior abdominal surgery influence conversion rates and outcomes of laparoscopic right colectomy in patients with neoplasia? *Dis Colon Rectum* 2008; **51**: 1669-1674 [PMID: 18622643 DOI: 10.1007/s10350-008-9278-4]

26 **Kwok SY**, Chung CCC, Tsang WWC, Li MKW. Laparoscopic resection for rectal cancer in patients with previous abdominal surgery: A comparative study. *Annals Of The College Of Surgeons* (Hong Kong) 2004; **8**: 115-119

27 **Aytac E**, Stocchi L, Ozdemir Y, Kiran RP. Factors affecting morbidity after conversion of laparoscopic colorectal resections. *Br J Surg* 2013; **100**: 1641-1648 [PMID: 24264789 DOI: 10.1002/bjs.9283]

28 **Keus F**, de Jong JA, Gooszen HG, van Laarhoven CJ. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. *Cochrane Database Syst Rev* 2006; **(4)**: CD006231 [PMID: 17054285 DOI: 10.1002/14651858.CD006231]

29 **Reza MM**, Blasco JA, Andradas E, Cantero R, Mayol J. Systematic review of laparoscopic versus open surgery for colorectal cancer. *Br J Surg* 2006; **93**: 921-928 [PMID: 16845692 DOI: 10.1002/bjs.5430]

30 **Noel JK**, Fahrbach K, Estok R, Cella C, Frame D, Linz H, Cima RR, Dozois EJ, Senagore AJ. Minimally invasive colorectal resection outcomes: short-term comparison with open procedures. *J Am Coll Surg* 2007; **204**: 291-307 [PMID: 17254934 DOI: 10.1016/

j.jamcollsurg.2006.10.002]
31 **Ellis H**. The causes and prevention of intestinal adhesions. *Br J Surg* 1982; **69**: 241-243 [PMID: 7042032]
32 **Liakakos T**, Thomakos N, Fine PM, Dervenis C, Young RL. Peritoneal adhesions: etiology, pathophysiology, and clinical significance. Recent advances in prevention and management. *Dig Surg* 2001; **18**: 260-273 [PMID: 11528133]
33 **Coleman MG**, McLain AD, Moran BJ. Impact of previous surgery on time taken for incision and division of adhesions during laparotomy. *Dis Colon Rectum* 2000; **43**: 1297-1299 [PMID: 11005501]
34 **Van Der Krabben AA**, Dijkstra FR, Nieuwenhuijzen M, Reijnen MM, Schaapveld M, Van Goor H. Morbidity and mortality of inadvertent enterotomy during adhesiotomy. *Br J Surg* 2000; **87**: 467-471 [PMID: 10759744 DOI: 10.1046/j.1365-2168.2000.01394.x]
35 **Pandya S**, Murray JJ, Coller JA, Rusin LC. Laparoscopic colectomy: indications for conversion to laparotomy. *Arch Surg* 1999; **134**: 471-475 [PMID: 10323418]
36 **Veldkamp R**, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy AM. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; **6**: 477-484 [PMID: 15992696 DOI: 10.1016/S1470-2045(05)70221-7]
37 **Croce E**, Olmi S, Azzola M, Russo R, Di Bonifacio M. Laparoscopic colectomy: indications, standardized technique and results after 6 years experience. *Hepatogastroenterology* 2000; **47**: 683-691 [PMID: 10919012]
38 **Casillas S**, Delaney CP, Senagore AJ, Brady K, Fazio VW. Does conversion of a laparoscopic colectomy adversely affect patient outcome? *Dis Colon Rectum* 2004; **47**: 1680-1685 [PMID: 15540299]
39 **Tekkis PP**, Senagore AJ, Delaney CP. Conversion rates in laparoscopic colorectal surgery: a predictive model with, 1253 patients. *Surg Endosc* 2005; **19**: 47-54 [PMID: 15549630 DOI: 10.1007/s00464-004-8904-z]
40 **Kelly M**, Bhangu A, Singh P, Fitzgerald JE, Tekkis PP. Systematic review and meta-analysis of trainee- versus expert surgeon-performed colorectal resection. *Br J Surg* 2014; **101**: 750-759 [PMID: 24760684 DOI: 10.1002/bjs.9472]
41 **Thorpe H**, Jayne DG, Guillou PJ, Quirke P, Copeland J, Brown JM. Patient factors influencing conversion from laparoscopically assisted to open surgery for colorectal cancer. *Br J Surg* 2008; **95**: 199-205 [PMID: 17696215 DOI: 10.1002/bjs.5907]
42 **Vaccaro CA**, Rossi GL, Quintana GO, Soriano ER, Vaccarezza H, Rubinstein F. Laparoscopic colorectal resections: a simple predictor model and a stratification risk for conversion to open surgery. *Dis Colon Rectum* 2014; **57**: 869-874 [PMID: 24901688 DOI: 10.1097/DCR.0000000000000137]
43 **Aytac E**, Stocchi L, Remzi FH, Kiran RP. Is laparoscopic surgery for recurrent Crohn's disease beneficial in patients with previous primary resection through midline laparotomy? A case-matched study. *Surg Endosc* 2012; **26**: 3552-3556 [PMID: 22648125 DOI: 10.1007/s00464-012-2361-x]
44 **Naguib N**, Saklani A, Shah P, Mekhail P, AbdelDayem M, Alsheikh M. Short term outcomes of laparoscopic colorectal surgery in patients with perious abdominal operations, 10 years experience. *Surgical Endoscopy and Other Interventional Techniques* 2013; **27**: S97
45 **Huang CC**, Su CH, Ghen YC, Fan WC, Ma CJ, Huang CJ. The impact of previous surgery on clinical outcomes of laparoscopic colectomy for colorectal cancer. *Surgical Endoscopy and Other Interventional Techniques* 2013; **27**: S113
46 **Patel K**, Siddiqi N, Flashman KG, O'Leary DP, Khan JS. Laparoscopic colorectal surgery outcomes for patients with previous abdominal surgery. *Colorectal Disease* 2011; **13**: 30
47 **King A**, Bracey E, Flashman D, Senapati A, Skull A, O'Leary D. Does higher BMI and previous abdominal surgery affect the clinical outcome or the conversion rate in laparoscopic colorectal surgery? Prospective data from 255 consecutive cases. *Colorectal Disease* 2009; **11**: 23
48 **Gellona J**, Inostroza G, Miguieles R, Elena Molina M, Bellolio F, Urrejola G, Espinola D, Larach T, Zuniga JM. Predictive factors for conversion in laparoscopic colorectal surgery and impact on early postoperative period, an 848 patient case control study. *Surgical Endoscopy and Other Interventional Techniques* 2013; **27**: S319
49 **Brouquet A**, Bretagnol F, Soprani A, Valleur P, Bouhnik Y, Panis Y. A laparoscopic approach to iterative ileocolonic resection for the recurrence of Crohn's disease. *Surg Endosc* 2010; **24**: 879-887 [PMID: 19730944 DOI: 10.1007/s00464-009-0682-1]

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