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Biliary Complications – The "Achilles Heel" of Orthotopic Liver Transplantation

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Complicações biliares – o „tendão de Aquiles" da transplantação hepática

Palavras Chave
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Since orthotopic liver transplantation (OLT) is the standard of care for end-stage liver disease the number of transplant centers and the annual number of OLT performed has gradually increased. One of the principle technical advances of OLT has been the standardization of techniques for biliary reconstruction. Nevertheless, biliary complications still occur, and they are associated with significant morbidity and mortality. In the early years of transplantation, surgical revision was performed to address post transplantation biliary complications. More recently, ERCP has been demonstrated to be effective in the treatment of the majority off biliary complications after OLT with a lower complication rate and shorter hospital stay when compared with surgery, and not compromising the option of operation in case of failure [1]. However, in some cases ERCP might not result in a definitive treatment, and long-term follow-up data on outcomes and complications after ERCP in liver transplant patients is scarce [2]. In refractory or unsuccessful ERCP, a percutaneous approach or surgical treatment may be necessary.

Biliary complications after OLT include anastomotic strictures (AS), non-anastomotic strictures (NAS), bile duct stones (BDS), biliary leaks (BL) and other less common conditions. ERCP is the first-line treatment modality in the management of biliary complications and is successful in the majority of patients, with PTC reserved for situation in which ERCP is not successful. Management of biliary strictures constitutes the most challenging procedure for the endoscopist, and the optimal management has not been defined.

AS are usually short segmental areas of stenosis involving the ductal anastomosis, occur early, and are characterized by the formation of scar tissue at the anastomotic site. Technical problems are the most frequent cause of AS, which comprise up to 85% of biliary strictures diag-

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nosed after liver transplantation [3–5]. The two biliary anastomoses usually performed during OLT surgery are choledochocholedochostomy (CC) and Roux-en-Y choledochojejunostomy (CDJ), with CC being the preferred method. The application of ERCP is ideal for those patients with CC because of the accessibility of the common bile duct through the duodenum. Although technically challenging, performance of ERCP in patients with Roux-en-Y CDJ by experienced endoscopists can also result in successful resolution of biliary complications after liver transplantation [6]. In AS, multiple stents are placed in the bile duct with stent exchange and/or placement of additional stents every few months until the stricture resolves. Alternatively, FCSEMS may be used. The success rates of ERCP support an endoscopic approach as the first-line treatment of post-OLT AS [7–9] although its long-term impact on morbidity and mortality rates has not been fully established. Many of the studies cited have been retrospective; the few published prospective trials are limited by either small sample size or patient heterogeneity [10, 11]. To date, no prospective, multicenter, randomized trial designed to determine the optimal management of anastomotic strictures after liver transplantation has been reported.

NAS are long, are thought to be the result of ischemic injury to the duct, and may be associated with obvious vascular compromise (hepatic artery or portal vein occlusion) or secondary causes resulting in vascular injury (cytomegalovirus, ischemia time, ABO incompatibility). Ischemic strictures are more common in cases of cardiac death than conventional deceased donor liver transplant (DDLT). The natural history of NAS (hilar and/or diffuse intra-hepatic) strictures is less favourable, and these strictures are traditionally less responsive to nonsurgical therapies. Despite attempts at balloon dilation, debris removal, and stenting, some 30 ± 50% of patients undergo repeat transplantation or die as a result of this biliary complication [12]. In general, AS resolve within 3–6 months whereas nonanastomotic strictures require a long duration of therapy. AS after LDLT require longer stent therapy than in patients with conventional DDLT. Biliary stone disease is common after liver transplantation and may occur independently or in the setting of strictures due to impairment in biliary flow. The formation of multiple, long, and diffuse stones, known as biliary casts, is a unique form of stone disease in the setting of liver transplantation. The exact etiology of biliary cast disease is not known but it has been associated with ischemia and strictures. Stone management is similar to that in nontransplant patients with the potential need for cholangioscopy and other advanced techniques for casts or stones occurring above strictures. Rarely, patients with a Roux-en-Y hepaticojejunostomy may require percutaneous cholangioscopy with electrohydraulic or laser lithotripsy for intrahepatic stone removal.

Biliary leaks commonly complicate liver transplantation with a higher incidence in patients with a DCD and LDLT. They usually occur in the early postoperative period. Biliary leaks are typically treated with placement of a biliary stent to bridge the leak, usually with sphincterotomy. If there is an associated biliary stricture, the stricture can be carefully dilated, and one or more stents can be placed beyond both the stricture and the leak though this is usually avoided in the first few weeks following surgery. ERCP results in resolution of >85% of leaks. FCSEMS have been used in the treatment of biliary leaks considered to be refractory to conventional treatment. Despite improvements in endoscopic techniques, stents, and deep enteroscopy techniques, endoscopic therapy may not be successful or feasible in certain situations. Large anastomotic leaks (e.g., in the setting of hepatic artery compromise) may not heal with endoscopic therapy. Similarly, leaks from a perforation or compromise of a Roux-en-Y anastomosis may require surgery because of an inability to reach the anastomosis for definitive treatment.

In this month's issue of *GE Portuguese Journal of Gastroenterology* Alves et al. performed a single-center, retrospective study of patients who underwent therapeutic ERCP due to post-liver transplant biliary complications at a deceased donor liver transplantation centre in Portugal. The authors analysed 120 patients treated with ERCP for biliary complications after OLT over a period of 10 years, and reported efficacy and treatment-related factors associated with better outcomes. Overall, ERCP was successful in 46% and ineffective in 28% patients. Per complication, efficacy was superior for isolated bile duct stones (91%) and bile leaks (86) using similar methods as in non-transplant patients. The success rate for treating biliary stenosis was lower: AS (39%) and NAS (12%) moreover the presence of biliary stenosis was associated with lower chance of ERCP efficacy (OR = 0.2). Regarding the type endoscopic treatment, stents were placed in 57 (68%) patients with AS and 12 (71%) patients with NAS. Stents were removed or replaced after a mean time of 4.5 ± 2.6 months. Balloon dilatation was performed in 59 (70%) patients with AS and 11 (65%) with NAS.

The success rate of ERCP reported by is lower than published data available; however, it is not possible to compare the results reported by Alves et al. with the avail-

able literature since contrary to most data, the authors do not use a predefined protocol regarding endoscopic treatment, and treatment may differ during the observed period. Moreover, the retrospective nature of the study and the relatively small sample size (especially in NAS) does not allow to really evaluate the efficacy of ERCP in treating this type of complication.

In the treatment of biliary stenosis stent placement was preceded by an endoscopic dilation in most procedures. Studies comparing ERCP with dilation alone with ERCP with dilation and stent placement have concluded that serial dilation with stent placement leads to higher success rates (41% vs. 75%) [13, 14]. Moreover, Morelli et al. [15] reported a higher rate (87%) of AS resolution using a rapid stent exchange protocol, every 2 weeks until stricture resolution; however, the short follow-up period (mean 360 days) precludes conclusions about durability of success rate.

The study by Alves et al. reports for the first time the experience of a Portuguese transplant center. It is important that other centers in the country report their own results and ideally a multicenter national study should be performed allowing analysis of a higher number of patients, comparing different treatment strategies and results. In this context, future research using the application of endoscopic biliary dilation and stenting for post-OLT anastomotic strictures should not only focus on rates of success but should also evaluate the potential reasons for procedure-related failures. Besides the surgical technique, multiple factors including recipient, graft and post-operative course are involved in the formation of post-OLT biliary stenosis, so optimal management may involve not only improving endoscopic techniques but controlling the diverse risk factors. Keeping this in mind, integrating of the biliary endoscopist in the multidisciplinary transplant team should result in an improvement of results so that biliary complications may no longer be considered the "Achilles hell" of liver transplantation.

Disclosure Statement

The authors have no conflicts of interest to declare.

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