DOI:10.23873/2074-0506-2018-10-1-7-14

Endoscopic diagnosis and treatment of biliary complications after orthotopic liver transplantation

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Received: 27 September 2017

Accepted for publication: 9 October 2017

Aim. *The aim of the study was to investigate the endoscopic diagnostic and treatment techniques for biliary complications after orthotopic liver transplantation, their efficacy and safety.*

Material and methods. *The study was based on the results of endoscopic treatment of 29 patients with biliary complications occurred after orthotopic liver transplantation in N.V.Sklifosovsky Research Institute for Emergency Medicine in the period from December 2001 to January 2017.*

Conclusions. *The state-of-the-art methods of therapeutic endoscopy enable a successful treatment of most cases of biliary strictures and biliary-biliary anastomosis incompetence, thus achieving good long-term results using a minimally invasive methodology.*

Key words: orthotopic liver transplantation, biliary complications, anastomotic stricture, biliary anastomosis incompetence, biliary-duodenal stenting, endoscopic retrograde cholangiography

ABSs – anastomotic biliary strictures
BBA – biliary-biliary anastomosis
EPST – endoscopic papillosphincterotomy
ERCPG – endoscopic retrograde cholangiopancreaticography
LT – liver transplantation
MDP – major duodenal papilla
NABSs – non-anastomotic biliary strictures
OLT – orthotopic liver transplantation

Biliary complications after orthotopic liver transplantation (OLT) have the status of "Achilles' heel". At the start of liver transplantation (LT) development, these complications occurred in 50% of patients [1-3]. According to literature data, the mortality due to biliary complications ranges from 2 to 9.6% [4-5]. With the improvement of surgical technique, suture material and the introduction of new microsurgical technologies, the incidence of these complications has decreased, but still remains at a fairly high level and varies within the range of 8-35% [6-8].

The most common biliary complications after LT are strictures and biliary-biliary anastomosis (BBA) incompetence that are often combined with each other [5]. Post-transplant strictures of the bile ducts are usually classified into anastomotic biliary strictures (ABSs) and non-anastomotic (NABSs) strictures. ABSs are relatively short in the extent and respond quite well to endoscopic treatment (70-80% cases) [9-11]. NABSs often result from an ischemic and immunological damage, they are diffuse, refractory to endoscopic treatment, and characterized by a higher recurrence rate and a

high probability of the graft loss. In this regard, liver transplantation is the method of choice for NABS treatment [8, 12].

The endoscopic retrograde cholangiopancreaticography (ERCPG) yields an accurate diagnosis of the stricture level and anastomosis incompetence [13, 14]. The endoscopic treatment of post-OLT biliary strictures includes a repeated balloon dilatation, multiple biliary-duodenal stenting with one or more plastic stents or with a self-expanding stent [15-17]. However, in patients with a compensated stricture, the risk of recurrence remains high, making 18% [9].

The study objective was to investigate the endoscopic diagnostic and treatment techniques for biliary complications after orthotopic liver transplantation, their efficacy and safety.

Material and methods

In the period from December 2001 to January 2017, 386 OLTs were performed in N.V.Sklifosovsky Research Institute for Emergency Medicine, including 338 cases (87.6%) where choledochocholedochostomy was the method of biliary duct reconstruction.

Our study was based on the treatment outcomes of 34 patients (10.1%) with biliary complications occurred after OLT.

Indications for the endoscopic treatment were the signs of biliary hypertension and/or BBA incompetence identified by means of minimally invasive instrumental diagnostic techniques: ultrasonography, magnetic resonance cholangiography, and hepatobiliary scintigraphy.

The strictures of the bile ducts developed average on the 70th postoperative day, their onset time varied from 5 to 360 days; only in one case, the stricture developed at 82 months after OLT. In 32 cases, the

stricture of bile ducts developed within 3 postoperative months. The incompetence of biliary anastomoses was recorded at 2 to 30 postoperative days, mean at 13.9 ± 7.6 days.

ERCPG was performed in 33 patients; in one case, the examination was not performed due to the severity of the patient's condition. Four patients with NABS supposed refractory to endoscopic treatment were excluded from the study.

Thus, the endoscopic treatment was attempted in 29 patients, including 20 men and 9 women. The age of the patients varied from 31 to 62 years, the mean age being 48.9 ± 2.1 years.

The endoscopic treatment of ABS was performed using the method including the diagnostic ERCPG, endoscopic papillosphincterotomy (EPST), biliary-duodenal stenting or nasobiliary drainage and balloon dilatation.

All procedures were performed in an X-ray Operating Room using an intravenous sedation of the patient. Duodenoscopy was performed using a standard OLYMPUS TJF-160VR video duodenoscope. After the selective catheterization of bile ducts, the ERCPG and the final assessment of the stricture location and extent were performed. If the cannulation of the suprastenotic hepatico-choledochal department was not feasible, the "rendez-vous" technique was used. After an antegrade drainage of the biliary tract, a string was passed into the duodenum where it was captured with a polypectomy loop and led out through the endoscope channel.

Before the endoscopic treatment, papillosphincterotomy was mandatory to prevent the Wirsung's duct occlusion and to reduce the likelihood of post-operative pancreatitis. Nasobiliary drainage was performed in a patient displaying acute cholangitis manifestations (Fig. 1). For ABS dilatation, we used COOK dilatation balloons, 8 mm in diameter

when inflated. After expanding the "waist" of the balloon in the ABS area, an exposure equal to 0.5-1 minute was maintained, with a pressure in the balloon of 4-5 atm. Two to 3 dilatations were performed per one procedure.

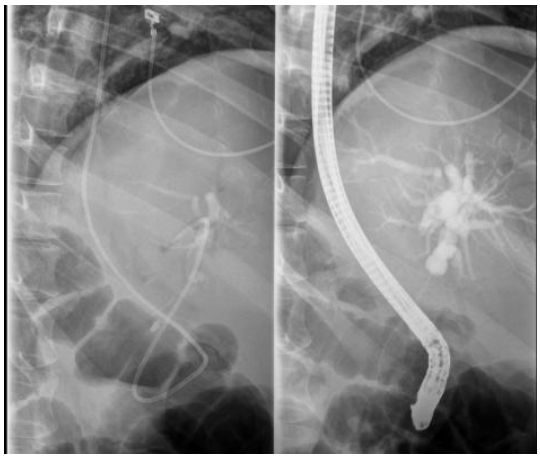

Fig. 1 . Cholangiogram: Nasobiliary drainage in the lumen of the bile ducts

For biliary tract stenting, the plastic biliary-duodenal stents of 7-11.5Fr diameter and 8-13 cm length, and the self-expandable fully covered metal stents of 0.8-1 cm in diameter and 8 to 10 cm in length were used.

Depending on the technical task, after passing the guide along the string, the proximal edge of the plastic stent was set at 1.5-2 cm above the ABS or into a hepatic lobar duct (in bilateral biliary-duodenal stenting) in a way that the distal end of the stent protruded into the duodenal lumen for 1-1.5 cm (Fig. 2-3). The metal self-expanding stent was positioned at 1.5-2 cm proximally to the ABS, and the distal end protruded into the duodenal lumen for 1 cm.

Fig. 2 . Cholangiogram: a plastic stent in the lumen of the bile ducts

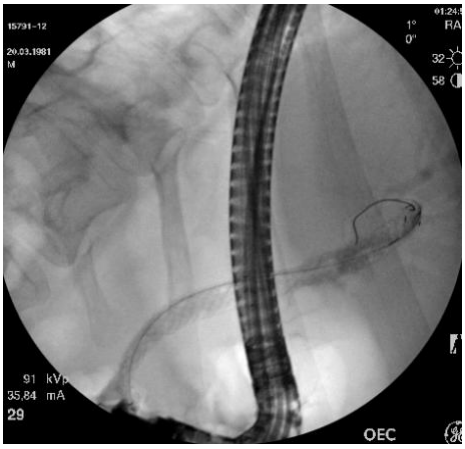

Fig. 3 . Cholangiogram: self-expanding fully covered metal stent in the lumen of the bile ducts

Endoscopic treatment was undertaken in stages. The planned replacement of plastic stents was performed after 2-3 months. In case of restenting with a metal self-expanding stent, the exposure was 4-6 months.

Criteria for endoscopic treatment efficacy included the resolution of biliary hypertension confirmed by mini-invasive instrumental diagnostic techniques (ultrasonography and others), and the duration of relapse-free course. The treatment outcomes were analyzed using standard descriptive

statistics methods. The duration of relapse-free course in patients with ABSs treated endoscopically was analyzed using the Kaplan-Meier method.

RESULTS

Among 29 patients, the ABS was detected in 21 (72.4%) patients, the ABS combined with BBA incompetence in 7 (24.1%); one more patient had a BBA incompetence (3.5%).

Transpapillary intervention was planned in 29 patients (100%). Cannulation of the major duodenal papilla (MDP) was successful in 22 of them (75.8%); in 7 other cases (24.2%) the attempts to cannulate the MDP failed. However, in 2 cases (6.9%), the suprastenotic biliary tract drainage was achieved using the anteretrograde "rendez-vous" technique, which resulted in biliary-duodenal stenting with a plastic stent.

The endoscopic treatment was not feasible in 5 patients (17.2%). The suprastenotic bile duct drainage was impossible due to a stricture with a diameter of less than 0.1 cm, which was combined with a significant angular (S-shaped) deformity of the anastomosis area (Fig. 4), which required surgical decompression.

Fig. 4. Cholangiogram: the marked angulation of the biliary-biliary anastomosis area

Thus, the number of patients who underwent endoscopic treatment was 24, or 82.8% of the group with BBA complications.

Biliary-duodenal stenting was performed with a plastic stent in 15 patients (51.7%) (Fig. 5), with a self-expanding fully covered metal stent in 2 (6.9%). Five patients (17.2%) underwent nasobiliary drainage to treat the acute cholangitis manifestations. After coping with purulent cholangitis 3-5 days later, the drainage was replaced with a plastic biliary-duodenal stent.

In 1 case (3.5%), the BBA incompetence without associated ABS, successfully resolved after biliary-duodenal stenting.

The plastic stent was replaced with a self-expanding one in 9 of 22 patients (40.9%) after a preliminary balloon dilatation of ABS (Fig. 5). In 13 patients, the plastic stent was replaced with another stent of the similar type.

Fig. 5 . Endoscopic photo: the distal edge of the plastic stent in the duodenum lumen

The mean period of the endoscopic treatment was 12 ± 1.9 months, the mean number of endoscopy procedures per patient was 2.5 ± 1.3 (from 1 to 6).

Owing to the staged endoscopic treatment, the ABS remission was achieved in 16 patients (55.1%), including 4 of them (13.8%) in whom BBA incompetence was successfully resolved, which accounted for 47.1% of all BBA area complications. The mean duration of relapse-free course was 40 ± 28 months (Fig. 6).

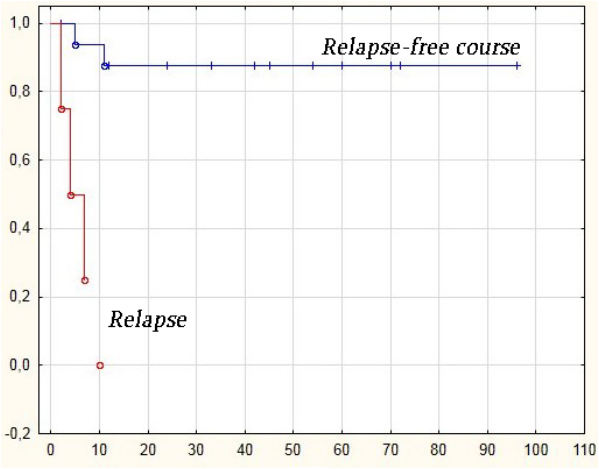

Fig. 6. The duration of relapse-free course in patients with ABS who underwent the endoscopic treatment, as analyzed by Kaplan-Meier method

Thus, the endoscopic treatment was successful in 17 (70.8%) of 24 patients. Despite the treatment course, the ABS relapse requiring a surgical intervention occurred in 7 patients (29.2%). The mean time to the onset of severe stricture relapse in the patients who underwent the endoscopic treatment was 5.7 ± 3.5 months (median 5.5 months). In the course of treatment, 1 patient (3.5%) died from the causes related to biliary complications.

Biliary tract strictures can cause serious clinical problems, up to severe biliary infection, sepsis, and the occurrence of graft secondary biliary cirrhosis [18].

For a long time, the endoscopic treatment of biliary strictures, either post-LT ones or any others, was limited to the placement of plastic stents. Thuluvath et al. [19] in their study demonstrated satisfactory treatment outcomes for the strictures that developed during the first posttransplant year

and were treated by making one or two balloon dilatations and choledoch stenting with a plastic stent, followed by its restenting every 2-3 months. However, the main drawback of plastic stents currently used remains the occlusion that inevitably occurs at 3 to 6 months later, as reported in a number of studies. A planned replacement of the plastic stent is required every 3 months to avoid the adverse effect on the graft [20]; meanwhile, the risk of complications, including infection-related ones, sill persists, especially in the immunocompromised patients who underwent OLT. Studies aimed at increasing the stent lifespan have led to the implementation of metal mesh constructs that may improve the patency and provide a reliable reinforcement, but have several drawbacks, the main of which being the tissue ingrowth due to reactive hyperplasia [21, 22]. With the advent of self-expanding fully coated nitinol stents in the endoscopy arsenal, new opportunities and prospects have emerged for the endoscopic treatment of biliary complications after OLT. Their efficacy and safety are currently still being investigated [23].

The modern concept of the posttransplant stricture treatment is based on the use of mini-invasive sparing techniques. Most strictures of the bile excretory anastomoses are successfully cured using mini-invasive or surgical techniques. The novel options present in the medical arsenal such as the balloon dilatation and self-expanding coated biliary stents significantly increase the liquidity of the endoscopic treatment methods. The endoscopic treatment inefficacy is the indication to a surgical intervention.

Our study results have demonstrated the efficacy and safety of the staged endoscopic treatment in the majority of patients with a post-OLT anastomotic stricture and(or) BBA incompetence. The whole complex of diagnostic and therapeutic transpapillary interventions developed for patients

with post-OLT biliary complications includes ERCPG, EPST, the bougienage and balloon dilatation of BBA strictures, if necessary, the prosthetics with plastic stents and their subsequent replacement with self-expanding fully coated metal stents at 3-6 months later.

Conclusions

1. Endoscopic retrograde cholangiopancreatography remains a highly informative method for diagnosing all biliary complications after liver transplantation.

2. Therapeutic tactics for biliary complications occurring in the biliary-biliary anastomosis area presupposes the priority of endoscopic treatment techniques. Modern methods of endoscopy and interventional radiology make it possible to successfully treat most cases of biliary strictures and the biliary-biliary anastomosis incompetence, thereby achieving good long-term results with a minimally invasive method.

3. Endoscopic treatment enabled to restore the patency of biliary-biliary anastomosis in 70.8% of patients after orthotopic liver transplantation and provided the relapse-free period of anastomotic biliary strictures for more than 2-5 years.

4. Inefficacy of endoscopic treatment is an indication to surgical intervention.

Conflict of interest. Authors declare no conflict of interests.

Financing. The study was performed without external funding.

References

1. Starzl T.E., Marchioro T.L., Vonkaulla K.N., et al. Homotransplantation of the liver in humans. *Surg Gynecol Obstet*. 1963;117:659–676. PMID:14100514

2. Calne R.Y. A new technique for biliary drainage in orthotopic liver transplantation utilizing the gall bladder as a pedicle graft conduit between the donor and recipient common bile duct. *Ann Surg*. 1976;184(5):605–609. PMID:791164

3. Neuhaus P., Blumhardt G., Bechstein W.O., et al. Technique and results of biliary reconstruction using side-to-side choledochocholedochostomy in 300 orthotopic liver transplants. *Ann Surg*. 1994;219(4):426–434. PMID:8161269

4. Fleck A., Zanotelli M.L., Meine M., et al. Billiary tract complication after orthotopic liver transplantation in adult patients. *Transplantat Proceed*. 2002;34(2):519–520. DOI:10.1016/S0041-1345(02)02615-5

5. Grief F., Bronsther O.L., Van Thiel D.H., et al. The incidence, timing, and managment of biliary tract complication after orthotopic liver transplantation. *Ann Surg*. 1994;219(1):40–45. PMID:8297175

6. Qin Y.S., Li Z.S., Sun Z.X., et al. Endoscopic management of biliary complications after orthotopic liver transplantation. *Hepatobiliary Pancreat Dis Int*. 2006;5(1):39–42. PMID:16481280

7. Na G.H., Kim D.G., Choi H.J., et al. Interventional treatment of a biliary stricture after adult right-lobe living-donor liver transplantation with duct-to-duct anastomosis. *HPB (Oxford)*. 2014;16:312–9. DOI:10.1111/hpb.12151

8. Olisov O.D. Biliary complications after orthotopic liver transplantation. *Transplantologiya. The Russian Journal of Transplantation*. 2009;(2):44–50. (In Russian).

9. Alazmi W.M., Fogel E.L., Watkins J.L. et al. Recurrence of anastomotic biliary stricture in patients who have had previous successful endoscopic therapy for anastomotic narrowing after orthotopic liver transplant. *Endoscopy*. 2006;38(6):571–574. DOI:10.1055/s-2006-925027

10. Mocchegiani F., Vincenzi P., Lanari J., et al. Immunological risk factors in biliary strictures after liver transplantation. *Ann Transpl*. 2015;20:218–224. DOI:10.12659/AOT.892393

11. Traina M., Tarantino I., Barresi L. et al. Efficacy and safety of fully covered self-expandable metallic stents in biliary complications after liver transplantation: a preliminary study. *Liver Transpl*. 2009;15(11):1493–1498. DOI:10.1002/lt.21886.

12. Buis C.I., Hoekstra H., Verdonk R.C., Porte R.J. Causes and consequences of ischemic-type biliary lesions after liver transplantation. *J Hepatobiliary Pancreat Surg*. 2006;13(6):517–524. DOI:10.1007/s00534-005-1080-2

13. Katsinelos P., Kountouras J., Paroutoglou G., et al. The role of endoscopic treatment in postoperative bile leaks. *Hepatogastroenterology*. 2006;53(68):166–170. PMID:16608016

14. Zhao Q., Chen Z.S., Qin H., et al. The role of endoscopic retrograde cholangiopancreatography in the diagnosis and therapy of biliary complications after orthotopic liver transplantation. *Chin J Organ Transplant*. 2004;25(5):291–293. DOI:10.3760/cma.j.issn.0254-1785.2004.05.011

15. Thuluvath P.J., Pfau P.R., Kimmey M.B., Ginsberg GG. Biliary complications after liver transplantation: the role of endoscopy. *Endoscopy*. 2005;37(9):857–863. DOI:10.1055/s-2005-870192

16. Morelli J., Mulcahy H.E., Willner I.R., et al. Long-term outcomes for patients with post-liver transplant anastomotic biliary strictures treated by endoscopic stent placement. *Gastrointest Endosc*. 2003;58(3):374–379. PMID:14528211

17. Morelli G., Fazel A., Judah J., et al. Rapid-sequence endoscopic management of posttransplant anastomotic biliary strictures. *Gastrointest Endosc*. 2008;67(6):879-885. DOI:10.1016/j.gie.2007.08.046

18. Granov A.M., Granov D.A., Zherebtsov F.K., et al. Liver transplantation. A single center experience of 100 cases. *Russian Journal of Transplantology and Artificial Organs*. 2012;(4):11–16. (in Russian).

19. Thulavath P.J., Atassi T., Lee J. An endoscopic approach to biliary complications following orthotopic liver transplantation. *Liver Int*. 2003;23(3):156–162. PMID:12955878

20. Kahaleh M., Behm B., Clarke B.W., et al. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? *Gastrointest Endosc*. 2008;67(3):446–454. DOI:10.1016/j.gie.2007.06.057.

21. Isayama H., Komatsu Y., Tsujino T., et al. A prospective randomised study of “covered” versus “uncovered” diamond stents for the management of distal malignant biliary obstruction. *Gut*. 2004;53(5):729–734. PMID:15082593

22. Shim C.S., Lee Y.H., Cho Y.D., et al. Preliminary results of a new covered biliary metal stent for malignant biliary obstruction. *Endoscopy*. 1998;30(4):345–350. DOI:10.1055/s-2007-1001280

23. Ryu S.N., Lee S.K. Biliary Strictures after Liver Transplantation. *Gut Liver*. 2011;5(2):133-142. DOI:10.5009/gnl.2011.5.2.133.