Analysis on biliary complications after orthotopic liver transplantation using biliary tract endoscopy★

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Abstract

BACKGROUND: Biliary complications are a common cause of death in patients after liver transplantation, biliary endoscopic minimally invasive technique is gradually becoming an important tool to solve biliary complications following orthotopic liver transplantation.

OBJECTIVE: To analyze the literatures on the biliary tract complications after liver transplantation, and to demonstrate a clear role of bile duct endoscopy in biliary complications.

METHODS: Using "orthotopic liver transplantation, biliary complications, biliary tract, endoscope technique" in English for the search term, Pubmed database were searched between January 1980 and October 2008; Using "liver transplantation, biliary complications, bile duct cast, cholangioscopy" in Chinese for the search term, Vip Chinese Periodical Database and CNKI database were searched between 1994 and January 2009. Literature language was limited to English and Chinese. The studies related to bile duct injury-caused biliary complications after liver transplantation were included, while other research unrelated to biliary complications after liver transplantation were excluded.

RESULTS AND CONCLUSION: A total of 52 literatures were screened out by the primary computer inspection, according to inclusion and exclusion criteria, 30 ones were involved for analysis. Biliary complications and vascular complications are considered as a common cause of death in patients after liver transplantation, particularly in biliary complications has become the major reason limiting the development of liver transplantation. Because of the difficulties on early recognition and treatment, the importance of the treatment for the complications in liver transplant patients is increasingly attracting more and more attention. Endoscopic operation technology and their subsidiary parts are improving, particularly therapeutic endoscopic retrograde cholangiopancreatography and biliary mirror technology are developing and continuously improving, biliary endoscopic minimally invasive technique is gradually becoming a major approach to solve biliary complications after orthotopic liver transplantation, The minimally invasive endoscopic diagnosis and treatment is an intuitive, reliable and credible means for the biliary complications after liver transplantation, serving as the most preferred method for diagnosing and treating biliary complications after liver transplantation.

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INTRODUCTION

In recent years, due to the improvements in surgical techniques and organ preservation techniques, as well as the use of new immunosuppressive agents, the survival rates of liver transplant patients have greatly improved[1]. But the rejection, biliary complications and vascular complications are still common cause of death in patients after liver transplantation, especially the incidence of biliary complication accounts for 5.8%–24.5%, it has become the main reason for restricting the development of liver transplantation[2]. With endoscopic operation technology and their subsidiary parts are modifying, biliary endoscopic minimally invasive technique is gradually becoming a major approach to solve biliary complications after orthotopic liver transplantation[3]. This article was aimed to analyze and summarize the clinical diagnosis and treatment of bile duct damage-caused biliary cast, clearly define the status and role of biliary endoscopy in biliary casting complications, from the perspective of biliary endoscopy, we can understand the pathological changes following the bile duct damage in an intuitive and objective manner, so as to provide guidance for the diagnosis and treatment of bile duct damage, as well as prognosis determination.

DATA AND METHODS

Literature source

Using "orthotopic liver transplantation, biliary complications, biliary tract, endoscope technique" in English for the search term, Pubmed database were searched between January 1980 and October 2008; Using "liver transplantation, biliary complications, bile duct cast, cholangioscopy" in Chinese for the search term, Vip Chinese Periodical Database and CNKI database were searched between 1994 and January 2009. Literature language was limited to English and Chinese. The studies related to bile duct injury-caused biliary complications after liver transplantation were included, while other research unrelated to biliary complications after liver transplantation were excluded.

Selection criteria

Design: Clinical research.

Participates: Patients with biliary tract complications following liver transplantation.

Types of intervention: The studies related to bile duct injury-caused biliary complications after liver transplantation were included, while other research unrelated to biliary complications after liver transplantation were excluded.

Outcome measurement indices: ① the pathological changes of bile duct damage. ② the imaging changes of bile duct casting materials/stone imaging changes.

Data extraction and quality evaluation of literature

Three evaluators carefully read the title, abstracts and full text of all documents received, so as to determine the literature met the inclusion criteria, and cross checked, if the differences occurred, they would

discuss or be assisted by the first researchers to solve.

RESULTS

Literature search results and quality evaluation

A total of 52 literatures were obtained through computer primary check by reading the titles and abstracts, including 15 Chinese ones and 37 English ones. Among them, 13 unrelated to this article for research purposes, 5 studies with repetitive contents, and 4 Meta analysis were excluded, finally 30 literatures were involved in the review.

Comprehensive analysis of documentary evidence

Types of biliary complications

Biliary fistula is consisted of anastomotic leakage and non-anastomotic fistula; anastomotic fistula is located in the donor and recipient bile duct anastomosis site, it occurrence is mainly related to the surgical approach, vascular complications and rejection; non-anastomotic fistula is mainly T-tube drainage fistula and T-tube fistula. Pfau *et al*[4] reported that among 31 cases of biliary fistula, 20 cases were affected in the anastomosis site, accounting for 74.1%, 7 cases in T-tube, accounting for 25.9%, an average time of biliary fistula occurring was 12 weeks in 31 cases.

Biliary stricture, including anastomotic stricture and non-anastomotic stricture, early anastomotic stricture is mainly related to surgical techniques, due to the improved surgical techniques in recent years, the causing stricture significantly decreased; non-anastomotic stricture is mainly related to ischemia and rejection, most of them are manifested as multiple extrahepatic bile duct stricture[5]. Later biliary stricture and obstruction is a common complication, anastomotic stricture is more common than non-anastomotic stricture, Yang *et al*[3] reported 14 patients with bile duct stricture by a comprehensive diagnostic cholangiography and 13 anastomotic stricture cases by biliary endoscopy (92.86%, of which 1 case was a stone-caused stricture illusion); Rerknimitr *et al*[6] reported 55 cases of bile duct stricture were consisted of 43 cases of anastomotic stricture, accounting for 78.2%, and 12 cases of non-anastomotic stricture, accounting for 21.8%, the average time of occurring bile duct stricture was 8.3 months.

Biliary obstruction, including bile duct casting material/stones, gallbladder sludge and Oddi sphincter dysfunction[7-13]. Bile duct casting materials/stones and biliary sludge often co-exit with bile duct stricture, gallstones occur later, associating to poor bile flow after biliary stricture, both receptor and donor bile duct can occur, but predominant in the donor. Rerknimitr *et al*[6] reported 46 cases of bile duct casting materials/stones, with an average emergence time of 19.2 months, of them 31 cases were accompanied simultaneously with bile duct stricture or biliary fistula, gallstones were mostly located in the proximal end of stenotic bile duct. Oddi aphincter dysfunction may be related to the approach of reconstructing nerve and bile duct controlling receptor bile duct and have been surgically resected, the incidence rate was 3%–7%[4].

Imaging diagnosis of biliary tract complications

Casting stones/bile duct casting materials/stones: MRCP (biliary water imaging) is rapid and non-invasive, it can provide three-dimensional reconstruction images of bile duct. Yang *et al*[14] reported 100% sensitivity and specificity of bile duct expansion by MRCP, but ineffective in the diagnosis of biliary fistula, bile duct stricture, casting stones, bile duct stricture accompanying casting stones. Biliary endoscopy (including endoscopic retrograde cholangiopancreatography, biliary endoscopy, peroral cholangioscopy) is orthophoric, objective, scientific, and minimally invasive, it can intuitively understand the lesions and the whole picture of bile duct, such as bile duct wall, pathology of bile duct mucosa, bile duct stricture, casting stones, *etc*[15].

T-tube angiography is a frequently used method for biliary tract surgery, but ineffective for the diagnosis of biliary complications after liver transplantation, because of its uniqueness and easy misdiagnosis, resulting in the offset of the treatment direction. Cholangiography has altered special performance at different phases of biliary complications after orthotopic liver transplantation[9]: early stage (1–3 months), there are a large number of floc biliary tract, especially fully covered, T-tube angiography exhibits that the entire biliary tree is often slightly smeared, without clear sheet or strip stone negative shadow, nor specific signs of bile duct expansion, thus easily overlooked, once T-tube drainage becomes poor or slightly impeded, the bile traits are not good, many sediments and floss are found in biliary drainage bag, bile drainage dose doesn't change much, is often confused by biliary tract infection, which is a common cause of misdiagnosis.

Three months later and even longer, the floss slowly coagulate into entities, forming cord-like, columnar, dendritic stones and even cast stones, these stones have not only resulted in the presence of biliary obstruction and varying degrees of expansion, but also easily lead to long-term, repeated, gradually aggravated infection, obstruction and jaundice, causing the biliary duct hardening and liver damage. At this phase, T-tube contrast images are relatively clear and specific, showing cord-like, flake and dendritic negative shadow, intrahepatic bile duct imaging is unclear or absent. Bile duct mildly expands, even shows serious signs of sclerosing cholangitis - bile duct stricture become thin and straight, bead-like, dry branch-like changes, endoscopic performance includes that the stone is full of bile duct, visual field is unclear, the stones are brown, resilient, cord-like, columnar, dendritic, rough surface, and there is a large number of tenacious honeybombs, with hollow and hierarchical on cross-sections[15-21]. Due to these characteristics, the contrast agents enter and adhere on the stones, layers and hollows, resulting in an irregular stone negative shadow, showing sheet-, weeping willow-, cord- and dendritic-shapes, the contrast agent discharge delays, while bile duct wall is not smooth, some small and single bile duct stones can easily be concealed, leading to a misdiagnosis[22]. Thus, T-tube angiography can not be satisfied with conventional methods, in case of doubtful outcomes and negative results, biliary tract endoscopy is suggested to perform as early as possible.

Single stone are clear in and out of liver and bile ducts, without sclerosis or stricture, encoscopic performance shows slight bile duct mucosal damage and good repair, the infection symptoms disappear, liver function quickly recovers, AKP, GGT, TBIL, IBIL rapidly decline and even recover to normal. If the disease is ignored or misdiagnosed, no endoscopic therapy is given, the stones would still remain in the biliary duct, leading to repeated

biliary tract infection and finally becoming a real reason for the stones, gradually forming new stones, leading to repeated obstruction, jaundice and infections, increasing the transplanted liver injury[23-28]. Compared with a single lesion, the multiple and casting lesion is more complicated, because these two types of bile duct mucosal damage are heavier, endoscopic observation shows bile duct mucosa has been completely or partly ablated, especially the transplant liver Ⅰ, Ⅱ grade bile duct, together with repeated long-term biliary tract infections, gallbladder wall inflammation becomes heavier and mucosal repair can be very long[19, 29-30].

Bile duct stricture: T-tube angiography/ERCP is an important means of diagnosing bile duct stricture, but T-tube angiography alone is not enough to determine the stricture. Due to the existence of multiple stones and casting stones, there is little or no contrast agent entering the intrahepatic bile duct, showing the segmental bile duct non-anastomosis stricture, segmental sheet negative shadow, dry branches, even intrahepatic bile duct disappearance with the absent intrahepatic bile duct, the physical analysis of the stones taken out through endoscope shows that, the segmental non-anastomosis stricture, segmental sheet negative shadow and dry branches are the specific manifestations of multiple stone and casting stones. The harvested stones shows good bile duct imaging, while non-anastomosis segmental stricture, bile duct loss syndrome and dry branches-like changes all disappear, biliary endoscopic selective angiography shows a clear imaging of biliary tree[3, 23]. Therefore bile duct loss is caused by the donor-receptor biliary anastomotic stricture, and extrahepatic bile duct cast materials/stone: the stricture and bile duct loss are not true, only the special post-transplant stone manifestations.

Endoscopic treatment of biliary tract

Biliary fistula: Treatments of biliary fistula include carunculae major sphincterotomy, nasal drainage and stent placement through the orificium fistulae, the selection of the treatment depends largely on the type and location of biliary fistula. Pfau *et al*[4] have reported the efficiency of endoscopic therapy in 31 patients with biliary fistula was 83.9%, T-tube fistula treatment was better, accounting for 95.2%, while the efficiency of anastomotic fistula treatment was only 42.9%. Non-anastomotic fistula is mainly at T-tube drainage, carunculae major sphincterotomy, nasal drainage can make the majority of fistula closed, few ineffective patients can be treated by stent placement through orificium fistulae. Or alone line carunculae major sphincterotomy and decompression also enable the majority of fistula closed.

Biliary stricture and obstruction: Biliary stricture after liver transplantation is mainly at bile duct anastomosis, then the anastomotic stricture is the focus of prevention and treatment[3]. Because those cord-like or columnar stones still exist, the obstruction will continue to occur, it is reported in the literature that nearly 20% of them ultimately need a surgery[24]. Endoscopy is satisfactory to obtain clinical results, that is clearly defining the type and extent of the stricture, and solve the stricture. Indwelling T-tube has a good preventive effect on the stricture, especially for the donor-recipient bile duct is relatively smaller or the diameter is uneven, also provides an approach for the diagnosis and treatment of postoperative cholangioscopy. As for the cases exhibiting postoperative sticture and stones, biliary endoscopy technology provides a minimally invasive, convenient, safe and scientific treatment, in particular, cholangioscopy, can observe the extrahepatic bile duct lesions and perform effective stricture and stone taking out treatment, avoid the missed diagnosis and misdiagnosed caused by simple imaging, take out the bile duct cast materials/stones, correct stricture, smooth the bile duct and prevent the secondary infection induced by the remnant stones and biliary sludge, as well as newborn stone. A simple endoscopic expanding support for biliary stricture is very effective, but the support time is shorter than the previous bile duct stricture, according to stricture obstruction and biliary infection time, the mucosal healing can be seen under microscope by 2–6 months anastomotic stricture supported for 2 months, as for more than 6–8 months, the stricture combined stone is relatively longer, also needs longer supporting time[11].

For the patients with bile duct cast materials/stones, the stone removal does not mean the end of treatment, although the recent T-tube contrast imaging shows good bile duct without stricture, encoscopic observation showed the donor-recipient bile duct anastomosis inflammation, severe edema and poor shank ingression, which is consistent with endoscopic diagnostic criteria for the stricture, although T-tube angiography revealed no significant stricture, we should pay attention to the possibility of a stricture, if a support is neglected at this time, it will lead to a stricture.

For the simple anastomotic stricture, a support is necessary after the expansion, as for those who remain T-tubes, biliary microscopy technology can easily solve, as for the patients without T-tube, ERCP techniques and peroral cholangioscopy both can complete the treatment of the stricture, the stricture observation can be performed using peroral cholangioscopy, but it is not comparable in operation, patient's burden and tolerance, thus the physicians are required to focus on indwelling T-tube, in order to facilitate the latter stricture diagnosis and treatment.

CONCLUSION

biliary endoscopic technique not only has the diagnosis role, but also can achieve a desired therapeutic effect using various endoscope-assisted technology, also is minimally invasive, repeatable, and well tolerant. With the popularity of endoscopic techniques and the improved operation of clinical physicians, more and more patients with biliary complications after liver transplantation will benefit from this technique.

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What's already known: The mechanism underlying bile duct damage-caused biliary cast after liver transplantation is not fully clear, biliary endoscopy plays an important role in the diagnosis and treatment of biliary complications after liver transplantation.
What's this study added: Subsequent to liver transplantation, bile duct cast materials/stone results from bile duct damage, serious cast materials should be induced by the bile duct mucosa full-thickness sleeve-like shedding, after endoscopic removal, the bile duct damage-caused bile duct mucosa is shown to loss normal structure, and whether bile duct restore normal anatomy and physiology following the repair still need further research.

从胆道内镜角度分析和认识原位肝移植后的胆道并发症*

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摘要

背景：胆道并发症是肝移植后患者常见的死亡原因，胆道内镜微创技术正逐步成为解决原位肝移植后胆道并发症的重要手段。

目的：分析文献中关于肝移植后胆道并发症的阐述和论证，明确胆道内镜在胆管铸型并发症中的地位和作用。

方法：以 orthotopic liver transplantation, biliary complications, Biliary tract, endoscope technique 为检索词，检索 Pubmed 数据库(1980-01/2008-10)；以肝移植，胆道并发症，胆管铸型，胆道镜为检索词，检索维普咨询数据库(1994/2009-01)、CNKI 数据库(1994/2009-01)。文献检索语种限制为英文和中文。纳入肝移植后胆管损伤导致胆管并发症相关的内容。排除肝移植胆道并发症以外的研究。

结果与结论：计算机初检得到 52 篇文献，根据纳入排除标准，对 30 篇进行分析。胆道并发症是肝移植后患者常见死亡原因，由于早期识别困难及处理棘手，正越来越受到重视。治疗性 ERCP 和胆道镜技术，成为解决移植后胆道并发症的重要手段和首选方法。

关键词：胆道镜；肝移植；胆道并发症；胆管铸型；综述文献

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