Complications in hepato-pancreateo-biliary surgery

Multidisciplinary and interdisciplinary approach

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Summary, general discussion and future perspectives
Summary

This thesis describes several efforts to contribute to improved surgical outcomes for patients undergoing hepato-pancreato-biliary surgery. In Part 1 of this thesis, we addressed several multidisciplinary treatment options for bile duct injury following cholecystectomy. This is a daunting complication of one of the most frequently performed, often elective, surgeries in western countries. Morbidity and mortality after bile duct injury are high, emphasizing the importance of optimal treatment of this complication. In order to adequately select patients for major surgeries, one should be aware of the risks associated with a procedure, as well as the profits it may bring (e.g. increased survival). In Part 2 of this thesis, we explored this balance for a number of biliary diseases. Part 3 of this thesis focussed more on the prevention of postoperative complications, making use of an interdisciplinary approach. This part of the thesis describes first steps in the development of a programme to actively involve relatives of patients in postoperative care. The ultimate goal of this programme is to reduce postoperative complications and unplanned hospital readmissions.

Part 1 – Multidisciplinary management of bile duct injury

In the first part of this thesis, multidisciplinary treatment options for bile duct injury (BDI) are described. In Chapter 1, the long-term impact of BDI is discussed, based on a comprehensive literature review. The most important long-term complication following surgical treatment of major BDI is the occurrence of anastomotic strictures. Of 35 studies reporting long-term outcomes after surgical reconstruction of BDI, anastomotic strictures occurred in around 10-20%, with a median time to stricture formation of 11-30 months. For minor BDI, which is usually treated endoscopically and sometimes by percutaneous transhepatic drainage, reported long-term success rates vary between 90-97%. So, overall most BDI patients will achieve good long-term results. Remarkably, several studies suggest that quality of life may be impaired even after ‘clinically successful’ treatment.

In this chapter we also evaluated our own outcomes of percutaneous dilatation of anastomotic strictures, as there appeared to be little evidence on how to treat anastomotic strictures. We found that of 81 patients who underwent percutaneous dilatation, this treatment was successful in 62 (77%), after a median of 3 dilatations per patient. Of 24 patients who underwent surgical revision of their hepaticojejunostomy (either as first treatment of an anastomotic stricture or after failed PTBD dilatation), re-stricture occurred in 5 patients (21%). We suggest a ‘step-up approach’ for these patients, with percutaneous dilatation as the first step in treatment, and surgical revision as a next step.
Chapter 2 describes four patients who developed a rare late complication following cholecystectomy: migration of surgical clips or coils into the common bile duct, which then became a nidus for the formation of gallstones. This caused symptomatic choledocholithiasis and, in three of four patients, cholangitis. All patients could be managed successfully by endoscopic retrograde cholangiopancreatography with extraction of stones, clips and coils. Three out of four patients had sustained BDI at the time of cholecystectomy, suggesting that local inflammation, in these cases caused by bile leakage, increases the risk of foreign body migration.

The percutaneous-endoscopic rendezvous procedure is a joined intervention of an endoscopist and an interventional radiologist in order to restore bile duct continuity. In Chapter 3, we analysed outcomes of 47 patients with BDI who underwent a rendezvous procedure. We found that the procedure was technically successful in 94% of patients, and that the procedure with its successive progressive stent treatment had a long-term success rate of 55%. Even for the other 45% of patients who required surgical reconstruction somewhere in the course of treatment, the rendezvous procedure can be considered of added value, as it provided internal biliary drainage and thus functioned as a bridge to surgery in a majority of these patients. Morbidity of the rendezvous procedure was acceptable, with major complications (Clavien-Dindo grade 3) occurring in 18% of patients and no occurrence of life-threatening complications or procedure-related mortality. Of note, all procedures were performed by highly specialized endoscopists and interventional radiologists, in a tertiary referral center with a large experience in complex biliary interventions.

In patients who require surgical reconstruction, a Roux-en-Y hepaticojejunostomy is usually performed. The optimal timing of surgery for these patients is an ongoing topic of debate. Chapter 4 describes the results of a meta-analysis of 21 studies who reported outcomes following hepaticojejunostomy for BDI. As in these 21 studies 15 different definitions for ‘early’ or ‘delayed’ surgery were used, we contacted authors and requested individual patient data. When individual patient data were made available we recalculated outcomes according to the most frequently used time interval, which was <14 days for early reconstruction and >6 weeks for delayed reconstruction. Meta-analysis showed that short-term morbidity was highest in the intermediate time interval (2-6 weeks), while the risk of anastomotic strictures was lowest after delayed reconstruction. We therefore concluded that delayed surgical reconstruction seems preferable, and reconstruction in the intermediate interval should be avoided. Still, individual patient circumstances should always be taken into account.
Part 2 – Selecting the right procedure for the right patient

To make a biliary-digestive anastomosis, a Roux-en-Y hepaticojejunostomy is usually performed. A choledochoduodenostomy requires less alteration of the normal anatomy, and is thus a less extensive surgery. However, this type of anastomosis is believed to cause certain long-term complications, such as sump syndrome and reflux gastritis. In Chapter 5, we compared short- and long-term outcomes of these two types of biliary-digestive anastomoses. As a choledochoduodenostomy is only selectively performed, we matched 26 patients who underwent choledochoduodenostomy to 26 patients who underwent hepaticojejunostomy based on age, sex, ASA-classification, indication, history of abdominal surgery, bowel resections or acute cholecystitis or pancreatitis. We found that short-term complications were comparable, however, patients undergoing choledochoduodenostomy more frequently developed an anastomotic stricture (6 versus 2 patients). Furthermore, all six patients with a stricture after choledochoduodenostomy eventually required surgical re-intervention, while the 2 patients with a stricture after hepaticojejunostomy. Although the risk of sump syndrome was low (2/26 patients, 7.7%), choledochoduodenostomy still seems to be inferior to hepaticojejunostomy.

For premalignant conditions, whether or not a resection is worth the risk is greatly dependent on the risk of malignant transformation of the condition. In Chapter 6, we describe a retrospective cohort of all patients who underwent resection of a choledochal malformation (Todani type I to IV) in one of the eight academic hospitals in the Netherlands. As this surgery is almost always performed in academic hospitals, this study more or less represents the Dutch patient population. In a study period of 26 years, a total of 123 patients underwent resection for this premalignant condition, with most patients undergoing extrahepatic bile duct resection with Roux-en-Y hepaticojejunostomy. In this cohort, severe morbidity following resection was 22% and postoperative mortality was 2%. As the incidence of a biliary malignancy (cholangiocarcinoma or gallbladder carcinoma) appeared to be 11% at the time of surgery, we concluded that prophylactic resection remains indicated in patients with a choledochal malformation, despite the high morbidity and even mortality associated with the procedure.

In Chapter 7 of this thesis we assessed the risk of major hepatectomy for perihilar cholangiocarcinoma by performing a meta-analysis on reported morbidity and mortality rates after resection for these tumors. We compared outcomes of studies originating from Western countries and Asian countries, and from low- and high-volume centers. A total of 51 studies were included. Remarkably, the median annual volume per center was only 4 major hepatectomies per year. Furthermore we found that overall morbidity was higher in Western studies compared to Asian studies (63% versus 54%, p=0.048), as was postoperative mortality (90-day mortality: 12% versus 3%, p<0.001). After correction for geographical location, increasing hospital volume was associated with higher severe
morbidity. This may reflect a referral bias. These results call for further examination of treatment differences between Western and Asian hospitals, in order to learn from each other and optimize outcomes.

Chapter 8 was a retrospective analysis of patients with a “mid-bile duct cholangiocarcinoma”, a tumour arising from the common bile duct above the upper pancreatic border but below the biliary confluence. For these tumours, a local resection can be done to obtain negative resection margins. A more extensive pancreatoduodenectomy probably has a higher morbidity but also leads to a wider resection with more adequate lymph node assessment. We retrospectively analysed clinicopathologic characteristics, postoperative outcomes and survival of patients undergoing local resection or pancreatoduodenectomy for mid-bile duct cholangiocarcinoma, with patients undergoing pancreatoduodenectomy for distal cholangiocarcinoma as a reference group. Lymph node retrieval was significantly lower following local resection with a median of 5 lymph nodes. Despite this, local resection showed less morbidity and comparable survival to pancreatoduodenectomy. Local resection therefore seems an acceptable treatment for selected patients with mid-bile duct cholangiocarcinoma.

Part 3 – An interdisciplinary approach towards prevention of postoperative complications

In the third part of this thesis, an ‘out-of-the-box’ intervention to reduce postoperative complications is described. We developed a program in which relatives of patients undergoing major abdominal surgery were actively involved in postoperative care of their loved ones, with a focus on care activities that have the potential to reduce the risk of certain complications. Besides the potential to improve patient outcomes, such a programme is also patient friendly and therefore can improve quality of care on different levels at the same time.

In Chapter 9, we aimed to identify possible existing programmes for the active involvement of relatives in postoperative care by performing a systematic review of literature. We only included studies in which relatives actually participated in care, and identified 8 studies reporting on 5 programs, most of which were carried out in stroke patients. Because of the small number of studies available and the heterogeneity between intervention programmes we were unable to draw firm conclusions regarding the effectiveness of active involvement of relatives in care. However, this systematic review underlined a need for further evaluation of this subject as patient-and family-centred care is increasingly propagated, but evidence regarding this topic is lacking. We therefore developed and evaluated our own family involvement programme. Chapter 10 describes the process of this development as well as the rationale, available
evidence for the interventions used. Outcomes of focus groups and group discussions with nurses and doctors were described and give insight in the facilitators and barriers for the implementation of our program.

Our family involvement program is a multi-component intervention, of which the most important component is the participation of relatives in basic care, focusing on mobilization, breathing exercises, cognitive activities and oral hygiene. For this, they receive a task-oriented training and act under the supervision of a nurse. Furthermore, relatives can be present during ward rounds and have the opportunity of rooming in.

In Chapter 11, the results of a pilot study testing the feasibility of our family involvement programme are presented. In this study, we included 20 patients who underwent esophageal or pancreatic resection and had a relative who was willing and able to participate in the program and compared these patients with a control group of 20 patients. We found that the patients in the intervention group mobilized more (estimated difference for walking 170 meters/day, and for sitting 109 minutes/day), and showed more adherence to breathing exercises, oral hygiene and cognitive activities. Caregiver burden, measured with the validated CarerQoL-7d questionnaire, did not deteriorate over time during the study period. All relatives and patients involved in the program valued this program positively, as did the health care professionals involved. These results are promising and give rise to a larger study assessing the effect of this program on patient outcomes.
General discussion and future perspectives

Part 1 – Multidisciplinary management of bile duct injury

Both in this thesis and in scientific literature worldwide, the focus of research on BDI is mostly on ‘major’ BDI (complete transection or even resection of the common bile duct). However, ‘minor’ injuries (leakage from the cystic duct or small ducts from the liver bed) may just as well lead to considerable morbidity. In a selected, tertiary setting significant morbidity and a mortality rate of up to 1.4% has been reported following minor injury. (1) Treatment of type A BDI is aimed at lowering the pressure gradient between the common bile duct (CBD) and the duodenum. This is done by endoscopic retrograde cholangiopancreatography (ERCP), and there are two ways to achieve this: by performing a sphincterotomy or by inserting a plastic stent in the CBD. Both treatment options have their own advantages and disadvantages: a sphincterotomy possibly increases the risk of haemorrhage whilst placement of a plastic stent requires a second intervention to remove this stent. (2) Evidence regarding the best strategy at ERCP (stent or sphincterotomy) is lacking, and could be a subject of future research. (3) For major BDI, the percutaneous-endoscopic rendezvous procedure is a relatively new approach that can restore bile duct patency, as was demonstrated in Chapter 3. Different kinds of ‘rendezvous’ can also be used in biliary interventions: a laparo-endoscopic rendezvous procedure has been described in order to clear the common bile duct of stones during laparoscopic cholecystectomy. In this procedure, the surgeon inserts a guidewire through the cystic duct, which can be picked up by the endoscopist for easy access to the common bile duct. (4) Furthermore, the endoscopic ultrasound-guided rendezvous is increasingly often used by endoscopists for patients in whom cannulation of the papilla is difficult. (5)

In Chapter 4 we concluded that delaying surgical reconstruction for 6 weeks or more seems preferable with respect to the risk of postoperative morbidity as well as to long-term outcome. Delayed reconstruction allows for clinical optimalization of the patient, and often requires deviation of bile by percutaneous transhepatic biliary drainage (PTBD). PTBDs can drain bile either internally (into the duodenum) or externally (into a collector). Internal drainage is preferred but cannot always be achieved in the case of a complete transection. External drainage of bile will cause loss of fluids and electrolytes, with risk of dehydration and electrolyte disbalance. Moreover, the loss of bile acids means a disturbance in the enterohepatic circulation, and a lack of bile acids in the intestines can result in malabsorption and malnutrition. (6, 7) Therefore, repletion of bile is often applied in patients with large amounts of bile draining externally. However, there is no available evidence on when and how much bile to replete. Future studies
should elucidate this. Furthermore, attention should be paid to the administration route (orally or per feeding tube), as both can be very burdensome for the patient. Of course, also for BDI prevention is better than cure. Recently, some advances have been made with intra-operative visualization of the bile ducts with near-infrared fluorescence. This technique may provide a solution to identification of the cystic duct especially during difficult cholecystectomy. However, more evidence regarding its’ effectiveness is needed.

**Part 2 – Selecting the right procedure for the right patient**

In order to minimize the burden of invasive treatments, a shift towards minimally invasive interventions has been going on for long. This does not only incorporate a shift from open to laparoscopic surgery, but also a shift from surgical towards endoscopic or percutaneous interventions. The previously mentioned EUS-guided rendezvous procedure can also be used for the creation of an EUS-guided choledochoduodenostomy. This could be a minimally invasive alternative to the surgical choledochoduodenostomy or hepaticojejunostomy discussed in Chapter 5.

The exact mechanism of carcinogenesis in patients with a choledochal malformation remains unknown, but the most accepted theory is that reflux of pancreatic fluid into the common bile duct and consequently increased levels of proteolytic enzymes lead to inflammation and biliary epithelial damage. This may be the underlying mechanism for both the bile duct dilatation seen in CM, and for biliary dysplasia, eventually leading to invasive carcinoma. Accordingly, the presence of a pancreatobiliary maljunction (PBM) has been reported to be correlated to an increased risk of malignancy. Furthermore, the existence of occult pancreatobiliary reflux in the absence of PBM has been reported, which could explain the development of malignancy in patients with a normal pancreatobiliary junction.

In our national cohort study (Chapter 6), we were unable to assess the relationship between PBM and malignancy due to the absence of adequate imaging to evaluate the pancreatobiliary junction in a majority of patients. Recent developments in diagnostic methods to assess PBM, such as secretine-enhanced MRCP and determination of amylase levels in bile, could enable more accurate determination of PBM in future studies in order to elucidate its’ role in carcinogenesis.

In the absence of sensitive screening tools for biliary malignancies, ‘watchful waiting’ in patients with a choledochal malformation remains dangerous. Early stage tumours are rarely visualized on conventional imaging such as CT or MRI; biomarkers such as CEA or CA19.9 lack sensitivity as well as specificity, and recent attempts to develop targeted sequencing for inconclusive brush cytology or a liquid biopsy test for
cholangiocarcinoma have not yet been successful. If a reliable non-invasive screening tool for cholangiocarcinoma could be developed, it would be worthwhile to be able to identify those patients with a low risk of malignant transformation as these patients could then refrain from surgery and be closely followed-up instead.

The differences in surgical outcomes following major hepatectomy in Asian compared to Western counties found in Chapter 7 of this thesis call for a thorough evaluation of differences in perioperative care. Although tumour biology and patient characteristics may explain part of the observed differences in outcome, differences in policy regarding preoperative biliary drainage and portal vein embolization probably also play a role.(23)

Part 3 – An interdisciplinary approach towards prevention of postoperative complications

In order to assess the effect of our family involvement program on patient outcomes such as postoperative complications and unplanned readmissions, we are currently conducting the ARTIS trial (‘Activating Relatives To get Involved in care after Surgery’ - Netherlands Trial Registry NTR7611). This is a randomized controlled trial in which adult patients who are scheduled for major abdominal surgery and have a relative willing and able to participate are randomized to either follow the program, or to usual postoperative care. Our hypothesis is that our family involvement program can lead to a reduction in unplanned hospital readmissions, as well as a reduction in postoperative complications that are sensitive to basic care. Besides assessment of these quantitative outcomes, future research should also explore experiences of patients and families participating in this program, as well as reasons not to participate.

For family members, being present during ward rounds facilitates a more thorough understanding of everything that is going on with the patient. This is important, as health literacy has been associated with postoperative outcomes.(24, 25) In the course of this project, we also developed a mobile application for participants of our program. Besides registration of activities for research purposes, this app gives us another opportunity for health education.

Our family involvement program is generalizable to other specialties. However, the fact that most admissions to undergo major surgery are elective certainly contributes to the feasibility of our program, as this allows the family to arrange work or other obligations. We therefore believe that extrapolation of this program to other surgical specialties with an elective component (such as orthopaedic surgery, gynaecology or urology) may be an appropriate next step.

Another extension to the involvement of family members in care could be the involvement of family in prehabilitation. Prehabilitation entails physical exercise, a nutrition plan,
and lifestyle modifications in order to optimize the clinical condition of a patient prior to surgery. (26) Engaging not only patients, but also their relatives in the planning and execution of such interventions could improve compliance to a prehabilitation plan.
References