Optimizing strategies in pancreatic and hepato-biliary surgery

Mungroop, T.H.

Creative Commons License (see https://creativecommons.org/use-remix/cc-licenses):
Other

Citation for published version (APA):
CHAPTER 1

General Introduction and Outline Of Thesis
Hepato-pancreato-biliary (HPB) surgery covers surgical procedures for malignant, pre-malignant or symptomatic benign diseases of the liver, pancreas and biliary tract. HPB-surgery is complex surgery with a high risk of postoperative complications. For example, in pancreatic surgery, although mortality rates have decreased to below 5%, morbidity rates remain around 40-45%.\textsuperscript{1-3} In liver surgery, mortality rates are below 5% depending of the extent of the resection\textsuperscript{4-6}, but also with these procedures morbidity rates remain around 40%.\textsuperscript{7,8}

Enhanced Recovery after Surgery (ERAS) programs consist of perioperative strategies that aim to enhance the restoration of functional capacity after surgery. These strategies include optimal pain control, early mobilization, prevention of surgical complications, and an early oral diet. Typically, ERAS programs result in reduced length-of-hospital stay and hereby also reduced costs. Specific ERAS guidelines were written for pancreatic surgery\textsuperscript{9} as well as for liver surgery.\textsuperscript{10} Both guidelines have highlighted the need for studies on optimal analgesic therapy, especially for studies of continuous wound infiltration (CWI) versus epidural analgesia, after HPB surgery.

**AIM OF THIS THESIS**

This thesis aims to improve perioperative strategies in HPB surgery. **Part I** focusses on finding the optimal analgesic strategy and investigates the impact of continuous wound infiltration (CWI) versus epidural analgesia. **Part II** includes studies on one of the most threatening complications of pancreatic surgery: postoperative pancreatic fistula (POPF). **Part III** consists of studies on worldwide perioperative practices in liver surgery, fluid therapy, new-onset diabetes after pancreatoduodenectomy (PD), and outcome prediction in HPB surgery.

**Improvement of analgesic therapy**

Prevention of postoperative pain is of major importance for the recovery of surgical patients. For many years, epidural analgesia has been regarded as the international standard for perioperative pain control in abdominal surgery.\textsuperscript{11} However, there are several potential disadvantages to epidural analgesia. First, occurrence of perioperative hypotension with the need to administer vasopressors.\textsuperscript{12} Second, the rare risk of potentially devastating neurological complications.\textsuperscript{13} Third, failure rates in up to 30% of patients are reported, resulting in periods of inadequate analgesia.\textsuperscript{14} Fourth, the need for preoperative placement in awake patients. This is considered cumbersome by many patients, and sometimes even leads to refusal of epidural analgesia.\textsuperscript{15}

CWI is a less-invasive alternative compared to epidural analgesia. By means of two
to three ‘wound’ catheters local anesthetics are infused in the pre-peritoneal plane in the subcostal area. This method is combined with patient-controlled analgesia (PCA) with opioids, especially for the first 24 hours postoperatively. Until recently, CWI+PCA was only used as primary method of perioperative analgesia in selected high-volume centers in the United Kingdom and United States. Although some studies have been performed on this topic, showing excellent results with CWI, there is a gap of knowledge in the literature.

Studies investigating the effectiveness of CWI+PCA versus epidural analgesia within current clinical standards and with the use of patient-reported outcomes, are scarce. For this reason, we designed and performed the randomized controlled POP-UP trial which we describe in chapter 2.

Although many studies reported that CWI is an effective alternative to epidural analgesia, some studies reported inferior outcomes. These conflicting outcomes, which are even found in systematic reviews, may hamper further implementation. We hypothesize that these differences could be explained by different efficacy in the placement of the ‘wound’ catheters: pre-peritoneal versus subcutaneous. Therefore, in chapter 3 we describe a systematic review including all relevant studies of CWI versus active alternatives as well as placebo-controlled studies. In chapter 4 we review the methodology and outcome of a recent trial of CWI versus epidural analgesia in liver surgery, and assess the state of current evidence of CWI.

A novel addition to the method of CWI is a bolus injection of local anesthetic at the start of the surgical procedure. In chapter 5 we determine plasma levels of local anesthetic after pre-peritoneal bolus versus epidural bolus injection to assess if the plasma levels are below toxic threshold levels.

**Prevention of postoperative pancreatic fistula**

Postoperative pancreatic fistula (POPF) is one of the most threatening complications of pancreatic surgery. Clinically relevant POPF occur in up to 20% of patients in PD and are typically associated with increased hospital stay, costs, re-intervention rates, and mortality. Prediction of the risk of POPF can help to optimize individual treatment decisions (e.g., drain placement, use of prophylactic medication). For this reason, several POPF prediction models have been proposed. Other useful applications include evaluation of surgeons technical performance, risk-adjusted comparison of surgical outcome, stratification in randomized controlled trials, as well as (high-risk) subgroup analyses. These prediction models are typically built with single-center data, often lack adequate (geographical) external validation, and most of these models have not been implemented in daily clinical practice.

The Fistula Risk Score (FRS) by Callery et al. is the most cited and validated POPF
prediction model in PD.\textsuperscript{22} The FRS predicts POPF based on four factors: gland texture, pancreatic duct diameter, intraoperative blood loss, and definitive pathology. There is however evidence to suggest that this model might be improved. Blood loss, one of the predictors of the FRS, was not a significant predictor in several external validation studies.\textsuperscript{25, 26} In chapter 6 we analyze which factors are predictors of POPF in PD using a large multi-institutional dataset. We design a new model, the alternative Fistula Risk Score (a-FRS) without blood loss as a predictor.

As a next step, we perform in chapter 7 a validation and model updating study of the a-FRS in a pan-European cohort of minimally-invasive PD.

Since an adequate POPF prediction model is currently not available in distal pancreatectomy (DP), we attempt to design such a model in chapter 8. In this large multicenter study, we assess independent predictors of POPF after DP and design the Distal Fistula Score.

In chapter 9 we describe the multicenter randomized controlled CPR (‘Closure of the Pancreatic Remnant’) trial of the Dutch Pancreatic Cancer Group. In this study we assessed the impact of stump closure using a fibrin sealant patch on POPF after DP.

\textbf{Optimizing perioperative management}

Fluid and pain management during liver surgery (e.g., low-central venous pressure (low-CVP)) are classic topics of controversy between anesthesiologists and surgeons. Little is known about current worldwide practices. Goal-directed fluid therapy (GDFT) has been associated with reduced morbidity in high-risk surgery, but its impact in open liver resections is unclear.\textsuperscript{10, 27}

GDFT aims to preserve adequate tissue perfusion by optimization of cardiac output. On the other hand, low-CVP aims at reducing blood loss during surgery, as well as improvement of the surgical field. The potential short-term beneficial effects of low-CVP on the surgical field seem to be conflicting with numerous randomized controlled trials (RCTs) on the benefits of GDFT in other types of surgery.\textsuperscript{27, 28}

In chapter 11 we assess perioperative practices in liver surgery among and between surgeons and anesthesiologists worldwide. The results of this study can guide the design of future international studies.

Since there is conflicting evidence on optimal fluid strategy in liver surgery, in chapter 12 we describe the randomized controlled GALILEO trial on GDFT versus low-CVP in major open liver surgery.

Another complication after HPB surgery is new-onset diabetes mellitus after pancreatic surgery. Since the exact risk of this complication is unknown in PD, in chapter 13 we assess the risk of this complication with a systematic review of the literature.
Although several studies advise the use of risk models when counseling patients for HPB surgery\textsuperscript{29,30}, studies comparing these models to the surgeons’ assessment are scarce. In \textbf{chapter 14} we assess whether risk prediction models outperform surgeons’ assessment for the risk of complications in HPB surgery.

\begin{table}[h]
\centering
\begin{tabular}{|l|p{12cm}|}
\hline
\textbf{Chapter} & \textbf{Research questions} \\
\hline
Chapter 1 & N.a. \\
\hline
Chapter 2 & How effective is continuous wound infiltration compared to epidural analgesia for analgesic therapy in HPB surgery regarding patient-reported outcomes and pain scores? \\
\hline
Chapter 3 & Is there a difference in effectiveness between the main strategies for catheter placement (pre-peritoneal versus subcutaneous)? Are optimally placed wound catheters as effective as alternatives such as epidural analgesia? Are there other clinical benefits? \\
\hline
Chapter 4 & What is our assessment of a recently completed study on continuous wound infiltration? How do we assess current en future studies on CWI versus epidural analgesia. \\
\hline
Chapter 5 & What are the local anesthetic plasma levels after pre-peritoneal bolus injection compared to epidural bolus in HPB surgery? Are the plasma levels below toxic threshold levels and what can we say regarding effectivity? \\
\hline
Chapter 6 & Which factors are independent predictors of POPF after pancreatoduodenectomy (PD)? Is it possible to design and externally validate an alternative Fistula Risk Score, without blood loss as a predictor? \\
\hline
Chapter 7 & How does the a-FRS perform in a pan-European cohort for minimally-invasive PD? Is it possible to update the a-FRS to further optimize performance in both MIPD as well as open PD? Are there specific additional risk factors for MIPD who do not play a role in open PD. \\
\hline
Chapter 8 & Which factors are independent predictors of pancreatic fistula after distal pancreatectomy (DP)? Can we develop and validate the first fistula risk score for POPF in DP? \\
\hline
Chapter 9 & Is stump closure with a fibrin sealant patch effective for the prevention of pancreatic fistula after DP? What is the incidence of POPF in experienced centers for pancreatic surgery? \\
\hline
Chapter 10 & What are the worldwide practices of liver surgeons and anesthesiologists regarding fluid and pain management in liver surgery? Which controversies do currently exist in liver surgery? \\
\hline
Chapter 11 & What is the impact of a goal-directed fluid therapy versus restricted fluid management such as low-CVP during major hepatic surgery? \\
\hline
Chapter 12 & What is the incidence in the literature of new-onset diabetes after PD? \\
\hline
Chapter 13 & How do available risk models for complications in HPB surgery perform compared to surgeons’ assessment? \\
\hline
Chapter 14 & N.a. \\
\hline
\end{tabular}
\caption{Research questions}
\end{table}
REFERENCES


