Optimizing strategies in pancreatic and hepato-biliary surgery

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CHAPTER 14
Summary, General Discussion and Future Perspectives
SUMMARY AND GENERAL DISCUSSION

This thesis describes several optimizing strategies aimed to improve care and enhance recovery of patients undergoing hepato-pancreato-biliary (HPB) surgery.

Part I – Improvement of analgesic therapy
For many years, epidural analgesia has been regarded as the international standard for pain treatment in major abdominal surgery. Although some studies have advocated continuous wound infiltration (CWI) with local anesthetics, there seemed to be room for improvement of current available research. In some studies of CWI versus alternatives, patients were treated with suboptimal standards of care e.g., no enhanced recovery program was used or there was a suboptimal (epidural analgesia) control arm.

In chapter 2, a randomized controlled POP-UP trial of CWI versus epidural analgesia in HPB surgery is described. A total of 102 patients were analyzed for the primary outcome. Non-inferiority was shown regarding the primary endpoint, the mean Overall Benefit of Analgesic Score. This is a composite endpoint of pain scores, opioid side-effects, and patient satisfaction. The study showed no difference in adverse events or failure of analgesic therapy. The results of the study suggest that CWI is non-inferior to epidural analgesia in HPB surgery.

Although many studies demonstrated CWI to be an effective alternative to current standards, some studies reported inferior outcomes. We hypothesized that this heterogeneity could be explained by different efficacy between the two main strategies for placement of the infiltrative catheters: pre-peritoneal versus subcutaneous. The aim of the systematic review, described in chapter 3, was therefore to assess outcomes between pre-peritoneal and subcutaneous CWI catheters. After screening 2,283 studies, 29 RCT’s with 2,059 patients were included. The study found pre-peritoneal catheters to be more effective than subcutaneous catheters. Pre-peritoneal wound catheters seem to be equally effective for pain control as alternatives such as epidural analgesia. Besides, with pre-peritoneal CWI benefits were seen regarding recovery parameters and the method was associated with better satisfaction rates.

In chapter 4, we responded to a recent paper on CWI versus epidural analgesia in liver surgery. Although we pinpoint some methodological issues in this study, we also argue that there is no argument for routine application of epidural analgesia. In our opinion, the time has come to embrace CWI as routine analgesic therapy in abdominal surgery.

A novel addition to the technique of CWI, is a bolus of local anesthetic at the start of the surgical procedure, in the pre-peritoneal plane. During the POP-UP trial (chapter 2) an event suggestive of local anesthetic toxicity occurred, when the protocol was
not followed. Since it is unclear to what plasma levels this needle-bolus leads when done correctly, this study aimed to assess plasma levels after injection done according to protocol. This exploratory study was described in chapter 5. This study shows that the pre-peritoneal bolus results in serum bupivacaine concentrations well below the commonly accepted toxic threshold. With CWI more additional analgesics are needed intraoperatively as compared to epidural analgesia. However, a reduction of intraoperative vasopressor usage was seen with CWI.

Part II – Prevention of postoperative pancreatic fistula

Postoperative pancreatic fistula (POPF) is often seen as the most threatening complication after pancreatic surgery. Preventing this complication or, at first, identifying a high-risk group could optimize treatment and enhance patient recovery. Current prediction models were typically built with single-center data, often lacked the use of sound statistical methods as well as (geographical) external validation. This could be the reason that most have not been widely implemented in daily practice. In chapter 6, the design and validation of the alternative Fistula Risk Score (a-FRS) for pancreatectoduodenectomy (PD) is described. Blood loss, one of the predictors of the original-FRS, the most cited and validated POPF risk model, was not a significant factor during recent external validation studies. The a-FRS was developed with (nationwide) data of over 1,900 patients after PD. The model is based on pancreatic texture, pancreatic duct diameter and BMI. The model was successful at international multicenter external validation.

Minimally-invasive pancreatectoduodenectomy (MIPD) is becoming increasingly popular because of its potential to enhance postoperative recovery compared to open PD. The a-FRS (chapter 6) was not yet validated for laparoscopic, robot-assisted, or hybrid MIPD. Therefore, the purpose of the study described in chapter 7 was to perform a validation and model updating study of the a-FRS in a large international cohort of MIPD patients. Initial validation showed the original a-FRS had moderate discrimination (AUC 0.68) for grade B/C POPF after MIPD. Calibration was inadequate, with systematic underestimation of the risk of POPF. After addition of male sex as a predictor, the updated a-FRS performed equally well in the subgroups of laparoscopic, robot-assisted, and hybrid MIPD as well as in open PD. In addition, single-row pancreatojejunosomy, as compared to other anastomotic techniques, was found to be independently associated with a substantially increased risk (OR 4.6) of POPF in laparoscopic MIPD. We therefore recommend that this technique should be discouraged until proven safe.

Currently, there is no adequate risk model available for POPF prediction in distal pancreatectomy (DP). In chapter 8, a prediction model for POPF after DP was developed including 625 patients. The Distal Fistula Score consists of three preoperative available variables: body mass index, pancreatic neck thickness, and pancreatic duct size. The last
two variables were measured at the preoperative imaging. The model performed well to predict POPF preoperatively and was also successful at external validation.

The use of absorbable fibrin patches has been investigated in pancreatic surgery for several years. Available older reports suggested a possible benefit of fibrin patches for reduction of POPF. Although some RCTs had been published on this topic, there were some methodological issues associated with these studies. The objective of the CPR trial, described in chapter 9, was to investigate whether an absorbable fibrin sealant patch could prevent POPF after DP. The study shows that POPF occur in 22% of patients after DP. This indicates that POPF remain a serious cause of morbidity in DP even in experienced pancreatic surgery centers. However, application of a fibrin patch on the pancreatic stump does not reduce the incidence of POPF.

Part III – Optimizing perioperative management
Since the liver is one of the best perfused organs of the human body, major liver surgery is associated with significant risk of blood loss and high morbidity rates. The correlation between the amount of blood loss and the risk of adverse outcomes in liver resections has been well established in several studies. Not all aspects of perioperative care in liver surgery, have been standardized.

For instance, fluid and pain management have been classic areas of controversy among surgeons and anesthesiologists. In chapter 10, the worldwide MILESTONE study was done including a total of 913 participants (495 surgeons and 418 anesthesiologists) from 66 countries. The study was supported by international organizations, such as the American Association of Anesthesiologists (ASA), Americas Hepato-Pancreato-Biliary Association (A-HPBA), International Hepato-Pancreato and Biliary Association (IHPBA), European-African Hepato-Pancreato-Biliary Association (E-AHPBA), and Australia-New Zealand Hepato-Pancreato-Biliary Association (ANZ-HPBA).

The study showed a large heterogeneity in fluid management practices as well as in pain management. Use of specific protocols for fluid therapy in liver surgery is low, since only 20% of the anesthesiologists have such a protocol for fluid therapy in liver surgery. 24% use a general protocol, and 55% have no protocol. The survey identified several areas of interest for future international studies. The large variation in practices demonstrated in this study is an interesting and possibly concerning finding, since in general large inter-provider variability is disadvantageous for patients.

Low central venous pressure (low-CVP) strategy is the current clinical standard for perioperative management during major liver resections. Low-CVP is aimed at reducing blood loss and thereby improving the quality of the surgical field. Goal-Directed Fluid Therapy (GDFT), on the other hand, aims at optimizing cardiac output for an individual patient and has been associated with reduced morbidity and mortality in major
abdominal surgery. RCTs using GDFT during the entire procedure of open major liver resections are scarce. In chapter 11 the GALILEO trial is described which compared the outcomes of perioperative GDFT versus low-CVP in liver surgery. Although GDFT led to a higher CVP, this did not lead to increased intraoperative blood loss or reduced quality of the surgical field suggesting its feasibility and safety in major liver resections.

Another relevant complication of HPB surgery is new-onset diabetes mellitus (DM) after pancreatic surgery. However, the exact incidence of this complication after PD is unknown in the literature. Therefore, the aim of the systematic review in chapter 12 was to assess the risk of new-onset DM after PD. After screening 1,523 studies, 22 studies involving 1,121 patients were included. The incidence of new-onset DM was 16%, and the rate of insulin-dependent DM was 6%. This is a clinically-relevant risk of DM after PD of which patients should be informed preoperatively.

Although several studies advocate the use of risk models when counseling patients for HPB surgery, studies comparing these models to the surgeons’ assessment are scarce. The aim of the study described in chapter 13 was to assess whether risk prediction models outperform surgeons’ assessment for the risk of complications in HPB surgery. This study showed that existing risk prediction models do not outperform surgeons’ assessment. Surgeons’ assessment outperforms most risk prediction models for liver surgery although both have a poor predictive performance for pancreatic surgery.

Table 1. Answers to the research questions

<table>
<thead>
<tr>
<th>Chapter</th>
<th>N.a.</th>
<th>Continuous wound infiltration (CWI) is suggested to be non-inferior compared to epidural analgesia in hepato-pancreato-biliary surgery, both regarding pain scores, as well as patient-reported outcomes.</th>
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<tbody>
<tr>
<td>Chapter 3</td>
<td>Pre-peritoneal wound catheters are more effective than subcutaneous catheters. Besides, pre-peritoneal CWI seems to be equally effective for pain control as alternatives such as epidural analgesia. Also, with pre-peritoneal CWI benefits were seen regarding recovery parameters and the method was associated with better satisfaction rates.</td>
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<td>Chapter 4</td>
<td>The study by Bell et al is largely underpowered. Future pain studies should include patient-reported outcomes. However, currently available evidence suggests that there is no argument for routine application of epidural analgesia in abdominal surgery.</td>
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<td>Chapter 5</td>
<td>A pre-peritoneal bolus results in serum bupivacaine concentrations comparable to epidural bolus injection and these are well below the commonly accepted toxic threshold. With CWI more additional analgesics are needed intra-operatively as compared to epidural analgesia.</td>
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<tr>
<td>Chapter 6</td>
<td>The alternative Fistula Risk Score was developed, based on pancreatic texture, pancreatic duct diameter and body-mass index. Blood loss could be omitted as a variable. This model was successful at international multicenter external validation.</td>
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<td>Chapter 7</td>
<td>The a-FRS was validated and updated in a pan-European cohort for minimally invasive pancreatoduodenectomy (MIPD). After addition of male sex as a predictor, the updated a-FRS performed equally well in all subgroups of MIPD subgroups as well as in open pancreatoduodenectomy (PD). In addition, single-row pancreateojunostomy in laparoscopy was found as a strong risk factor for postoperative pancreatic fistula (POPF).</td>
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<tr>
<td>Chapter 8</td>
<td>In distal pancreatectomy (DP), body-mass index, pancreatic neck thickness, and pancreatic duct size are independent predictors for POPF. The Distal Fistula Score was designed and was successful at geographical external validation.</td>
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<td>Chapter 9</td>
<td>Application of a fibrin patch on the pancreatic stump does not reduce the incidence of POPF. The incidence of POPF is 22% in experienced centers.</td>
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<td>Chapter 10</td>
<td>There is large heterogeneity in fluid management practices as well as in pain management in liver surgery. There is also a low use of fluid therapy protocols. Low-central venous pressure (low-CVP) is the most used strategy for fluid therapy. Epidural analgesia is the most used type of analgesic therapy.</td>
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<tr>
<td>Chapter 11</td>
<td>Although Goal Directed Fluid Therapy leads to a higher CVP in liver surgery, this did not lead to increased intraoperative blood loss or reduced quality of the surgical field. This suggests its feasibility and safety in major liver resections.</td>
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<tr>
<td>Chapter 12</td>
<td>The incidence of new-onset diabetes mellitus after PD was 16%. The incidence of insulin-dependent diabetes mellitus was 6%.</td>
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<tr>
<td>Chapter 13</td>
<td>Surgeons' assessment outperforms most risk prediction models for liver surgery. In pancreas surgery both risk models as well as surgeons' assessment have a poor predictive performance.</td>
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<td>Chapter 14</td>
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FUTURE PERSPECTIVES

The total amount of HPB procedures performed has steadily increased in the last decade.\textsuperscript{1, 2} This emphasizes the need for studies on this topic, to improve care and further enhance recovery of patients undergoing HPB surgery.

**Analgesia**

Our studies suggest that CWI is non-inferior to epidural analgesia in abdominal surgery, and might be beneficial regarding recovery parameters and patient satisfaction. In our opinion, there is currently sufficient evidence for the addition of CWI to the current analgesic repertoire. Compared to alternatives such as epidural analgesia but also transversus abdominis plane block, wound catheters are more easily placed. Also, CWI lacks the need for preoperative (often considered cumbersome) placement in awake patients and there is also no risk (on) of devastating neurologic complications such as epidural hematoma and abscess.

Future studies should focus on further validating CWI in procedure-specific RCT’s with large groups of patients. Such studies should focus on clinical recovery parameters, but also include patient-reported outcomes. Besides, implementation and training programs would be beneficial to increase the availability of this technique to more patients.

**Postoperative pancreatic fistula**

In this thesis, several prediction models for POPF were developed and updated both for PD as well as for DP. As with any clinical risk prediction tool, the (updated) a-FRS and Distal Fistula Score need to be further validated and updated if necessary. This warrants adequate risk prediction in the future and in different patient groups. Such studies should adhere to current guidelines for these studies\textsuperscript{3}, and involve large and high-quality multicenter datasets.

These models could offer a valuable tool to target preventive strategies for POPF in high-risk patients. The addition of extra variables to the models should be studied, always considering the effort-reward balance, especially with variables which are not easily available.\textsuperscript{4} An example of these are precise measurements on pre-operative imaging.\textsuperscript{5} Also, since the a-FRS is a intraoperative prediction model, a model based on pre-operative variables only would be of interest. Such a model could be used to start preventive treatment prior to surgery, or referral of high-risk patients to undergo surgery in expert centers. Although we attempted to do so in the a-FRS, this led to a substantially lower predictive ability of the model. This was mostly because of the strong independent predictive value of pancreatic texture. Future studies should therefore
attempt to determine or predict pancreatic texture preoperatively.

Besides, future studies should investigate the benefits of using the prediction models to improve individual health outcomes and cost-effectiveness of care. This should preferably be done within a RCT to guide decision-making in high-risk patients. Also, quality improvement projects and benchmarking are sensible directions for future research.

Regarding fistula mitigation strategies, future research should focus on novel strategies. This is especially rewarding in high-risk patients, since the absolute risk reduction can be the largest in these patients. Promising novel strategies include perioperative hydrocortisone administration and botulinum toxin injection in the sphincter of Oddi. Multicenter RCT’s are needed to validate if these interventions are indeed as effective as sometimes suggested in smaller (non-)randomized studies.

Fluid therapy
The MILESTONE study shows that there is large and consistent heterogeneity of fluid therapy practices in liver surgery. Well-designed trials are necessary on these key issues in order to standardize and improve care of patients undergoing liver surgery. Since the use of specific fluid therapy protocols is currently low, there might be room for improvement on this matter. As a result of the GALILEO trial, a larger (multicenter) trial should be performed to further assess the impact of GDFT on postoperative complications and the surgical field in major liver resections.
REFERENCES


