Review Article

Clinical Highlights in the Treatment of Pancreatic Diseases

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Abstract

Despite advances in the treatment of pancreatic diseases, they remain clinical challenges. In this review article, the author summarized the key abstracts presented at 9th Congress of the European Hepato-Pancreato-Biliary Association, held in Cape Town, South Africa, from April 12th to 16th, 2011. These studies include the endoscopy, surgery, complications, and other clinical points of the pancreatic treatment.

Keywords: Chronic pancreatitis, Complications, Duodenal perforation, Pancreatic surgery

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Endoscopic Duodenal Perforations

Duodenal perforation is a rare complication of endoscopic retrograde cholangiopancreatography (ERCP). It is associated with significant morbidity and mortality. The aim of one study was to evaluate the management and outcome of these perforations considering the type of injury and method of treatment-conservative versus surgical. Between 1995 and 2010, a total of 1638 ERCP procedures were performed. Twenty-nine duodenal perforations (1.7%) were identified and reviewed. Patients' median age was 73 years. Nineteen patients had ductal stone disease. In 23 cases the diagnosis of perforation was made within 24 h following the procedure. Sixteen patients were treated surgically and 13 conservatively. Of the surgically treated patients, ten were operated on immediately following diagnosis. Overall mortality was 31%. Delay of operation and/or inappropriate procedures were identified in eight out of the nine mortality cases. Two out of four patients with type I (lateral duodenal) perforations who had early surgery survived. Ten patients were diagnosed as type II (peri-Vaterian) injury. Of them, three patients were operated on immediately and survived; out of the seven patients managed initially conservatively four had died. Only two patients out of seven with type III (bile duct) injury failed conservative management and all five patients with type IV (retroperitoneal air) perforations survived without an operation. Most patients that survived surgical treatment had complex duodenal diversion procedures. It was concluded that early diagnosis is a crucial factor in the management of ERCP related duodenal perforations. Most of type III and type IV injuries can be managed conservatively. Retroperitoneal fluid on computed tomography (CT), delay in diagnosis and failure of conservative treatment requiring surgical intervention are associated with poor outcome. Early aggressive surgery may improve outcome in type I and type II injuries. Duodenal diversion should be the procedure of choice.[1]

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Operation of Chronic Pancreatitis

The reliability and validity of the European Organization for Research and Treatment of Cancer's quality of life (QoL) questionnaire (QLQ-C30, version 3) in clinical studies of patients with chronic pancreatitis (CP) before and after the local resection and lateral pancreatico-jejunostomy (LR-LPJ) or Frey procedure was endorsed in 1995. This procedure was performed for symptomatic and/or complicated chronic pancreatitis. The poor socioeconomic conditions from which the indigent South African presents may influence the long term outcome after this procedure. To compare pre- and

post-LR-LPJ outcomes using the QLQ-C30 and to compare it to a locally developed structured interview a prospective, observational, long-term study was conducted. Consecutive adult patients with a confirmed diagnosis of painful and/or complicated CP undergoing the procedure were included. 112 LR-LPJ procedures were performed between 1995 and 2009. Sixty-five participants answered the QLQ-C30 and were interviewed at follow ups (months of follow up: mean: 24, range: 0.5–141). Fifty-two of these answered both instruments within 6 months after surgery, 32 before and after the surgery. Post-LR-LPJ there were significant improvements in QLQ global health status: (27 points, *n*=31), and emotional (15 points, *n*=32) and social (21 points, *n*=32) functioning, but not with physical functioning (0.85 points, *n*=2). Their improvement in role functioning was clinically relevant but not significant (15 points) and cognitive functioning was neither clinically relevant (improved 8 points) nor significant. Mean functional scale scores improved postoperatively in the 32 (12 points). There was a clinically relevant improvement in most symptom scales of the QLQ-C30. Pre- and post-surgical mean symptom scale scores improved by 17 points (*n*=32). There were no significant differences in the means of the functional (1 point) and symptom (3 points) scale scores between postoperative (≤6 months) and final (minimum of 6 months) visits (*n*=52). There was poor agreement between the QLQ-C30 pain score and the visual analogue scale for pain of the interview. Significant improvements in most domains of the QLQ-C30 post operatively were found. For patients (*n*=32) with QLQ-C30 measurements preoperatively the improvement to last visit was significant for mean functional and symptom scale scores, while for patients (*n*=52) with QLQ-C30 measurements postoperatively but within 6 months improvement to last visit was not significant, suggesting that benefits were mostly made manifest within 6 months. Apart from pain there was concurrence between some parameters of the QLQ-C30 and the structured interview.[2]

Centralization of Pancreatoduodenectomies

Mortality after pancreaticoduodenectomy (PD) may be reduced by nationwide centralization of this complex procedure to high volume centers. In the Netherlands, the first initiative to centralize PD dates back to 1997. Evaluation of this process in 1999 and 2005 showed no change in referral patterns or decrease in mortality. It was evaluated the current state of centralization and mortality of PD in the Netherlands in the period 2004-2009. Data were retrieved from the independent, nationwide registry (Kiwa Prismant Utrecht, The Netherlands) for ICD-9 code 5-526 (pancreaticoduodenectomy, including Whipple). Hospitals were categorized by number of annually performed PDs based on previously published data: <5, 5-10, 11—16, and >16 PDs. Number of PDs per hospital and associated mortality in the period 2004-2009 were evaluated. In 2004, 295 PDs were performed by 48 hospitals compared to 343 PDs by 30 hospitals in 2009. The number of hospitals performing <5 PDs decreased from 23 to 8, as did the number of hospitals performing 5-10 PDs, from 17 to 7. Hospitals performing 11-16 PDs increased from 6 to 10 and likewise hospitals >16 PDs, from 2 to 5. Hospitals meeting the recommended number of at least 11 PDs performed 40% of the PDs in 2004 compared to 82% in 2009. PD associated mortality decreased from 11.5% in 2004 to 6.4% in 2009 which was a statistically significant difference. Average mortality during the 6-year period for categorized hospitals performing <5, 5-10, 11-16, or >16 PDs (2009 volume) was respectively 14.2%, 8.3%, 7.4%, and 5.4%. Thus it was concluded that centralization for PD in the Netherlands is succeeding and is associated with a reduction in postoperative mortality. Current efforts to further stimulate centralization and improve outcome include a new nationwide study group for pancreatic cancer, regional hospital network agreements and involvement of both the ministry of Health and insurance companies.[3]

The aim of one study was to determine long-term survival after pancreatoduodenectomy for cancer of the pancreatic head and to determine clinicopathologic features of long-term survivors. Between 1985 and 2004, a total of 1612 patients were diagnosed with cancer of the pancreatic head in the southern part of the Netherlands. Long-term survival was defined as ≥ 5 years survival after cancer diagnosis. Follow-up was at least 5 years or until death. Of the 1612 patients with pancreatic cancer, 233 (14%) underwent surgical resection. The 5-year survival rate of these surgical patients was 7.3% (*n*=7), including 10 patients (4.3%) who survived longer than 10 years. Mean age of the 17 long-term survivors was 65±9 years and 53% were men. No differences in patient and tumor characteristics were observed between the patients who underwent pancreatic resection who were still alive after 5 years (*n*=17) and those who died within 5 year follow-up (*n*=216). Notably, 3 out of 17 (18%) patients who underwent resection and survived during 5 years after diagnosis had tumor stage T3-4, 2 patients (12%) had a poorly differentiated tumor grade and 2 patients (12%) were diagnosed with positive local regional lymph node metastasis. The results confirm that patients with pancreatic head carcinoma have poor prognosis. However, 5-year survival after pancreatic resection is possible even in patients with an advanced T stage, poorly differentiated tumor grade and positive local regional lymph node metastasis.[4]

Boosted by high postoperative mortality, pancreatic surgery was centralized in the south of the Netherlands, a region characterized by the absence of academic centers. The impact of this initiative was investigated. All patients diagnosed in the Eindhoven Cancer Registry area in

the periods 1995-2000 (precentralization) and 2005-2008 (implementation of centralization agreements) with primary cancer of the pancreatic head or duct, extrahepatic bile ducts, ampulla of Vater, and duodenum were included (*n*=2129). Resection proportions, in-hospital mortality, and 2-year survival were analyzed. Multivariable regression analyses were used to discriminate independent risk factors for death, including changes in treatment patterns. Resection rates increased from 19% to 30%, a statistically significant difference. The number of hospitals performing resections decreased from 8 to 3, the annual number of resections per hospital increased from 2 to 16. In-hospital mortality rates dropped from 24% to 4%, reaching 0% in 2008. Two-year survival after surgery increased from 38% to 49%, which also was a significant difference. Two-year survival irrespective of treatment increased from 10% to 16%, but did not improve in the non-surgery group. After adjustment for relevant patient- and tumor factors, patients undergoing surgery after centralization exhibited a lower death risk (hazard ratio 0.70, 95% confidence limits 0.51-0.97). Changes in surgical referral patterns seemed to explain the improvements. It was concluded that high quality of care can be achieved in non-academic regional hospitals through collaboration. Centralization should no longer be regarded as a threat by general hospitals but as a chance to improve outcome for patients suffering from pancreatic cancer.[5]

Perioperative Fluid Restriction

A number of recent studies have shown beneficial effects of perioperative fluid restriction during intraabdominal surgery on various outcome parameters including complications, recovery of gastrointestinal function and duration of hospital stay. The aim of one study was to investigate whether intraoperative crystalloid fluid restriction in pancreatic surgery would have a beneficial effect on postoperative complications. The main endpoint was delayed gastric emptying (DGE), measured 7 days postoperatively by Technetium scan, as this is the most common complication. Secondary endpoints were postoperative complications, weight gain and duration of hospital stay. Sixty-six patients were randomized, and 50 patients completed the full protocol. Twenty-six patients were subjected to a restricted (R) fluid protocol (5 ml/kg/h) and 24 patients to a standard (S) fluid protocol (10 ml/kg/h), Ringers Lactate, during the operation. Postoperative fluid was set at 2.5 l/24 h in both groups. Thirty-three pancreatoduodenectomies (PD) and 17 double bypass (DBP) operations were performed. All patients underwent preoperative and postoperative gastric emptying scintigraphy. DGE occurred in 12 out of 26 patients in the R group and in 11 out of 24 patients in the S group. The time to empty half of the stomach contents (T½) was 194 min in the S group, and 170 min in the R group, which was not statistically different. Complications, weight gain and duration of hospital stay were comparable in both groups. Thus the results do not support the hypothesis of a beneficial effect of crystalloid fluid restriction during pancreatic surgery on DGE incidence or clinical outcome.[6]

Fast Track After Pancreatic Surgery

The concept of fast-track surgery allowing accelerated postoperative recovery is accepted in colorectal surgery, but efficacy data are only preliminary for patients undergoing major pancreatic surgery. It was aimed to evaluate the impact of a modified fast-track protocol in a high-volume center for patients with pancreatic disorders. Between 2005 and 2010, 154 subjects had resective pancreatic surgery and were enrolled in the program. Essential features of the program were no preanesthetic medication, upper and lower air-warming device, avoidance of excessive i.v. fluids perioperatively, effective control of pain, early reinstitution of oral feeding, immediate mobilization and restoration of bowel function following surgery. Outcome measures were postoperative complications, such as pancreatic fistula, delayed gastric emptying, biliary leak, intra-abdominal abscess, postpancreatectomy hemorrhage, acute pancreatitis, wound infection, 30-day mortality, postoperative hospital stay, and readmission rates. On average, patients were discharged on postoperative day 10 (range 6-69), with a 30-day readmission rate of 6%. Percentage of patients with at least one complication was 39%. Pancreatic anastomotic leakage occurred in eight of 107 pancreatico-jejunostomies, and biliary leak in three of 115 biliary jejunostomies. Postoperative hemorrhage occurred in ten (6%) patients and wound infection in nine (6%) cases. In-hospital mortality was 1.9%. Fast-track parameters, such as normal food and first stool, correlated significantly with early discharge. Multivariate analysis, lack of jaundice and resumption of normal diet by the 5th postoperative day were independent factors of early discharge. It was concluded that fast-tack programs are feasible, easy, and also applicable for patients undergoing major surgery such as pancreatic resection.[7]

Drain over the Pancreatojejunal Anastomosis

Pancreatic fistula (PF) is a leading cause of morbidity and mortality after pancreato-duodenectomy (PD). The aim of one multicenter prospective randomized trial was to compare the results of PD with an external drainage stent versus no stent. Between 2006 and 2009, 158 patients who underwent PD were randomized intraoperatively to either receive an external stent inserted across the anastomosis to drain the pancreatic duct (*n*=77) or no stent (*n*=81). The criteria of inclusion were soft pancreas and a diameter of wirsung <3 mm. The primary study end point was PF rate defined as amylase-rich fluid (amylase concentration >3 times the upper limit of normal serum amylase level) collected from the peripancreatic drains after postoperative

day 3. CT scan was routinely done on day 7. The two groups were comparable concerning demographic data, underlying pathologies, presenting symptoms, presence of comorbid illness, and proportion of patients with preoperative biliary drainage. Mortality, morbidity, and PF rates were 3.8%, 52%, and 34%, respectively. Stented group had a significantly lower overall PF (26% vs 42%), morbidity (42% vs 62%), and delayed gastric emptying (8% vs 27%) rates compared with nonstented group. Radiologic or surgical intervention for PF was required in 9 patients in the stented group and 12 patients in the nonstented group. There were no significant differences in mortality rate (3.7% vs 3.9%) and in hospital stay (22 vs 26 days). It was concluded that external drainage of pancreatic duct with a stent reduced pancreatic fistula rate and overall morbidity rates after pancreatoduodenectomy in high risk patients (soft pancreatic texture and a nondilated pancreatic duct).[8]

Intra-Abdominal Postoperative Drains After Pancreatic Resection

In several fields of abdominal surgery, postoperative use of abdominal drains was once considered standard practice. However, since accumulating evidence suggests that drains do not contribute to patients' wellbeing, prolong hospital stay and may even be harmful, the use of drains has been abandoned for most abdominal procedures. It was assessed whether there is also sufficient evidence to abandon postoperative drainage after pancreaticoduodenectomy for pancreatic malignancies. A systematic review of the evidence in PubMed and a heterogeneity-adjusted trial sequential meta-analysis was performed. The search produced 45 potentially relevant papers. Of these, two papers met our predefined inclusion criteria. The absolute difference in postoperative complication rate was 6% and 8%, respectively, favoring the no-drain group. A heterogeneity-adjusted sample size calculation showed that 814 patients are needed to demonstrate a 10% reduction in complication rate (from 30 to 20%). With the two studies that have been conducted, 11% and 33% of the required number of patients has been included. It was concluded that currently, there is insufficient evidence to conclude that postoperative use of abdominal drains after pancreaticoduodenectomy results in a higher incidence of major complications. Taking into account the available evidence, a further 550 patients need to be enrolled in future trials investigating the usage of abdominal drains after pancreaticoduodenectomy. A randomized clinical trial investigating this topic is currently prepared in the Netherlands.[9]

Prophylactic Gastroenterostomy in Non-Resectable Cases

The value of a prophylactic gastroenterostomy (usually combined with a biliary bypass) in patients with unresectable cancer of the pancreatic head is a subject of controversy. A systematic review of the literature (retro- and prospective studies) and a meta-analysis of the prospective studies on the use of prophylactic gastroenterostomy for unresectable pancreatic cancer were performed. Analysis of retrospective studies did not reveal a clear advantage/disadvantage for a prophylactic gastroenterostomy. Three prospective studies comparing a prophylactic gastroenterostomy plus biliodigestive anastomosis versus no bypass or a biliodigestive anastomosis alone were identified (altogether 218 patients). In the group of patients with a prophylactic gastroenterostomy, the chance of gastric outlet obstructions during follow-up was significantly lower (odds ratio, OR 0.06, 95% confidence interval 0.02 to 0.21), whereas the rates of postoperative delayed gastric emptying were comparable. There were no significant differences in morbidity and mortality. The length of hospital stay following prophylactic gastroenterostomy was estimated to be 3 days longer than for patients without bypass. It was concluded that prophylactic gastroenterostomy should be performed during the exploration of patients with unresectable pancreatic head tumors because it reduces the incidence of long-term gastroduodenal obstruction without impairing short-term outcome.[10]

Delayed Gastric Emptying

Delayed gastric emptying (DGE) is a frequent complication after pancreatoduodenectomy (PD). Some authors suggest that an antecolic (compared to retrocolic) route of the gastroenteric (GE) anastomosis lowers the incidence of DGE. To investigate the relation between route of GE-anastomosis and the incidence of DGE after PD a consecutive series of 203 prospectively recorded PDs were evaluated, and the route of GE-anastomosis was established by reviewing operation reports. Hospital course and follow-up were prospectively recorded. Patients with antecolic and retrocolic GE-anastomosis were compared. Main outcome measure was the incidence of DGE according to the International Study Group of Pancreatic Surgery criteria. Secondary outcome measures were other complications and hospital stay. In 47 patients the route of GE-anastomosis could not be determined. Two patients were excluded because they had Roux-en-Y reconstruction. Of the remaining 154 patients, 77 had a retrocolic anastomosis and 77 had an antecolic anastomosis. In the retrocolic group, DGE occurred in 58% of patients (grades: A, 25%; B, 17%; C, 17%). In the antecolic group, 52% had DGE (grades: A, 21%; B, 16%; C, 16%) (i.e. there was not a significant difference). "Primary" DGE (not due to other intra-abdominal complications) occurred in 36% of the retrocolic group and 20% of the antecolic group which was a significant

difference. "Primary" clinically relevant DGE (grade B/C) occurred in 18% and 10%, respectively. There was no difference in need for (par)enteral nutritional support, other complications, mortality or length of stay. The authors concluded that the route of GE-anastomosis had no influence on the overall incidence of DGE. Clinically relevant DGE (overall and "primary") was not different between the retrocolic and antecolic group. "Primary" DGE (any grade) was more frequent in the retrocolic group, mainly due to a higher incidence of DGE grade A. The preferred route for GE-anastomosis in PD remains to be confirmed in a well-powered randomized trial.[11]

Influence of Complications after Pancreatic Resection on the Long-Term Prognosis

Complications following pancreatic resections are a significant source of morbidity and may affect hospital stay. Patients with severe complication require further intervention. It was sought to ascertain whether significant complication following pancreaticoduodenectomy for ductal adenocarcinoma impacts on long term survival. The unit is a tertiary referral center for all hepatopancreato-biliary surgery and performs over 100 elective pancreatic resections annually. It was retrospectively examined patients undergoing Whipple's resection from 2002 to 2009. Postoperative complications were graded according to Clavien and pancreatic leaks were graded as per the International Study Group on Pancreatic Fistula (ISGPF) classification. Over the study period; in total 486 pancreaticoduodenectomies were performed; 190 (39%) of which were for pancreas ductal cancer. The complication rate for all was 33% (159/486), of which Clavien grade 1 comprised 16% (26/159), grade 2 were 42% (67/159), grade 3 were 18% (29/159), and grade 4 were 17% (27/159). There were eight perioperative deaths; i.e., mortality was 1.6%. The overall pancreatic fistula rate was 18% (85/486) with ISGPF grade A 24% (20/85), grade B 42% (36/85), and grade C 34% (29/85). After censoring for perioperative mortality, in the pancreatic ductal adenocarcinoma subgroup, the complication rate was 25% (46/186). Of these, 15% (7/46) were Clavien grade 3 or 4 and/or ISGPF grade C which were defined as significant complication. Median survival for ductal cancers was 25 months (95% confidence interval 20-31 months). Kaplan–Meier (univariate) analysis did not reveal any significant relationship between occurrence of complications including the occurrence of a pancreatic leak and long-term survival. It was concluded that postoperative complication and mortality rates in the series of patients are at comparable levels to other high-volume centers across the world. The occurrence of a serious postoperative complication does not appear to adversely influence long-term survival for patients with pancreatic ductal adenocarcinoma.[12]

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