

Original article

EVALUATION OF STANDARD HEPATICOJEJUNOANASTOMOSIS AS A SEQUENCE OF RECONSTRUCTION IN RADICAL PANCREATODUODENECTOMY - WHIPPLE PROCEDURE PROSPECTIVE RANDOMIZED SINGLE CENTER CLINICAL STUDY

ЕВАЛУАЦИЈА НА СТАНДАРТНАТА ХЕПАТИКОЈЕЈУНОАНАСТОМОЗА КАКО ДЕЛ ОД РЕКОНСТРУКЦИЈАТА КАЈ РАДИКАЛНАТА ПАНКРЕАТОДУОДЕНЕКТОМИЈА – ВИПЛОВА ПРОЦЕДУРА ПРОСПЕКТИВНА РАНДОМИЗИРАНА КЛИНИЧКА СТУДИЈА ОД ЕДЕН ЦЕНТАР

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Abstract

Introduction. Pancreaticoduodenectomy is a standard procedure for the treatment of pancreatic head carcinoma, although it may also be used for treatment of certain benign diseases of the pancreatic head. If the diagnosis is established at stage III or IV, the 5-year overall survival is about 3%. With the advance of diagnostic procedures, the disease is diagnosed at an earlier stage (I), resulting in an improved 5-year survival rates of up to 30-40%.

The aim of this study was to compare our results with those in published series using standard interrupted hepaticojejunostomy (HJA) and to identify risk factors influencing postoperative morbidity and mortality.

Methods. The study included 50 patients with pancreatic head carcinoma, who underwent hepatojejunostomy. All patients randomly received a straight biliodigestive anastomosis with interrupted sutures. We investigated the onset of biliary leakage (biliary fistula), occurrence/persistence of reflux cholangitis postoperatively beyond the 5th postoperative day, development of postoperative pancreatic fistula grades B or C, and length of postoperative hospital stay.

Results. Of all 50 patients, in one patient postoperative biliary leakage-postoperative biliary fistula (POBF) developed. The incidence of reflux cholangitis decreased significantly from 44 to 26. The mortality rate in the study was 6% (3 patients). One patient died from pulmonary thromboembolism, while 2 suffered POPF grade C, with consecutive multiorgan failure.

Conclusion. Further clinical trials are required to compare the results and to choose the most effective and safest suturing technique. However, according to the results of our study, hepatojejunostomy technique

is quite safe, effective, and represents a valuable option among other available techniques.

Keywords: hepaticojejunostomosis, standard anastomosis, biliary leakage, biliary fistula, onset/persisting reflux cholangitis

Апстракт

Вовед. Панкреатикодуоденектомија е суверена процедура за третман на карцином на главата на панкреасот, но може да биде и третман за некои бенигни заболувања на главата на панкреасот. Кога дијагнозата е поставена во III или IV стадиум, вкупното преживување од 5 години е околу 3%. Со напредокот на дијагностичките процедури во последно време, дијагнозата се поставува порано - I и II стадиум, а прогнозата се поправа до 30-40% за 5 години.

Целта на оваа студија беше да се споредат нашите резултати со резултати на објавени серии користејќи стандардна хепатојејуностомија (HJA) и да се идентификуваат факторите на ризик што влијаат на постоперативниот морбидитет и mortalitet.

Методи. Во студијата вклучивме и опериравме 50 пациенти со карцином на главата на панкреасот. Кај рандомизираната популацијата се направи стандардна термилолатерална билиодигестивна анастомоза со поединечни шевови. Следевме евентуална појава на билијарно истекување-билијарна фистула, појава/перзистирање на рефлуксен холангитис постоперативно во период пократок или подолг од 5-тиот постоперативен ден, постоперативна панкреатична фистула Б и Ц, времетраење на постоперативниот болнички престој. Резултати: од сите 50 пациенти, 1 пациент постоперативно доби билијарно протекување-постоперативна билијарна фистула (POBF). Рефлуксниот холангитис значително се намали од 44 на 26. Морталитетот во студијата бе-

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ше 3 случаи, 6%. Еден пациент почина од пулмонален тромбоемболизам, додека 2 страдаа од ПОПФ Ц, со последователна мултиорганска слабост.

Заклучок: потребно е да се направат дополнителни клинички студии за да се споредат резултатите и да се избере најсоодветната и најбезбедна техника за креирање на анастомозата. Сепак, според резултатите од нашата студија, стандардната техниката што ја користевме е безбедна, корисна и секако го зазема своето место меѓу другите техники.

Клучни зборови: хепатојејуноанастомоза, права анастомоза, билијарна истекување, билијарна фистула, почетен/перзистираан рефлуксен холангитис

Introduction

Pancreaticoduodenectomy, Whipple procedure, is a standard surgical treatment for malignant diseases and in certain cases benign diseases of the pancreatic head. Of all pancreatic carcinomas, approximately two-thirds (64%) arise in the head of the pancreas-pancreatic head carcinoma (PHC). Unfortunately, 50-60% of patients are diagnosed at advanced stages (III or IV), leading to a poor prognosis, with an overall 5-year survival rate of less than 10%. On contrary, when the diagnosis is made at an early stage of the disease (first or second stage), the survival rate increases to 36-40% [1]. Over the past decades, the devices and methods for early diagnosis have been significantly advanced, contributing to improved prognosis and outcomes. Nevertheless, there is still much to be done, as the accuracy of current diagnostic procedures is 85-90% [2]. It should also be noted that other benign diseases, i.e. chronic pancreatitis, IPMN, hormonally active NET, and cystadenomas, most frequently require surgical treatment when located in the pancreatic head.

Pancreaticoduodenectomy (PD) as a complex procedure is inevitably associated with postoperative morbidity, although it has significantly decreased recently. The major contributor to postoperative morbidity, eventually leading to mortality is clinically manifested postoperative pancreatic fistula (POPF), grades B or C. Its incidence was reported to be about 60 to 70% in the past, but currently it is reduced to 20-40% [3]. However, patients may also suffer from biliary leakage-biliary fistula (BF), due to insufficiency of the biliodigestive anastomosis. This biliary fistula usually occurs due to an impaired integrity of the suture line, particularly in cases when associated with local risk factors, including bacterial suppurative cholangitis, ischemia of the biliary stump caused by excessive dissection, small diameter of the common bile duct (CBD), and inadequate surgical technique resulting in tension and narrow anastomosis. BF is especially hazardous when

associated with POPF, as the two factors exert a supra-additive synergistic corrosive effect leading to severe destruction of the operative site (OS) [4]. The increased severity of this combination is based on the activation of proteolytic enzymes in pancreatic secretions, and if present, by bacterial infection which is frequently associated with pancreatic leakage.

Although technical failure is considered a relatively uncommon cause of BF, surgical technique remains a crucial factor, particularly in the hands of an experienced surgeon, who can compensate and neutralize other risk factors. So far, several techniques for creating biliodigestive anastomosis have been described: direct-straight anastomosis (SA) with interrupted sutures and SA with continuous suture, oblique-slant anastomosis particularly for narrow common biliary ducts, and the Hepp-Cuonaud procedure for perihilar anastomosis. A telescopic antireflux biliodigestive anastomosis with a single suture has so far been tested only in animal models [5].

The most important principals of biliodigestive anastomosis are:

1. Providing adequate vascularization of the biliary stump;
2. Creation of the widest possible biliodigestive anastomosis, if necessary, providing bigger diameter with oblique-slant incision, longitudinal anterior wall incision, or the Hepp-Cuonaud when appropriate;
3. Achievement of an R0 resection on the superior margin in cases of malignancy;
4. Construction of a tension-free anastomosis;
5. Use of monofilament 4-0 or 5-0 absorbable suture material;
6. Perfect adjustment between the jejunal and biliary mucosa;
7. Abundant irrigation of the biliary stump before anastomosis, particularly in patients with purulent cholangitis, which is frequently encountered after ERCP or PTC stenting.

The main objective of this study was to compare our results with those reported in studies using the technique of straight anastomosis (SA) with interrupted sutures as part of the pancreatoduodenectomy reconstruction. We also aimed to determine the risk factors associated with this anastomosis and to evaluate measures for reducing postoperative morbidity and mortality.

Material and methods

From 2014 to 2017, we operated 50 patients with PD, for PHC, distal cholangiocarcinoma, ampullary and perampullary carcinoma. The inclusion criterion for the study population was operable and resectable PHC. All patients were investigated and preoperatively staged at the University Clinic for Gastroenterohepatology. They underwent the following diagnostic proce-

dures: US, ERCP, CECT, MRI cholangiography, and measurement of tumor markers (CEA, CA 19-9, VEGF). A total of 46 patients underwent biliary stenting; 43 stents were placed during ERCP and 3 after PTC, to resolve the excessive and prolonged jaundice. Four

patients were referred directly for surgery without prior stenting. Of the 46 patients with biliary stent, 44(95%) developed bacterial cholangitis, confirmed with preoperative bile cultures. Tabela 1

Table 1. Distribution of patients in the groups depending on stenting of CBD

	Patients with stenting of the CBD	Patients without stenting of the CBD	Total
Patients received SA	46	4	50

The biliodigestive reconstruction during the Whipple procedure consisted of T-L HJA with interrupted sutures, 4-0, or 5-0, depending on the thickness-thinness of the biliary duct wall.

During the surgical procedure, microbiological samples were obtained, and the biliary stamp was repeatedly irrigated and flushed with saline solution until clear bile was obtained.

The used technique was imposed by the previously

determined characteristics of the common bile duct. Patients with a caliber of the CBD less than 6 mm underwent either an oblique-slant anastomosis or a longitudinal incision of the anterior wall though enlargement of the diameter of the anastomosis. Interrupted sutures were used, with full-thickness (perforating) bites through the CBD and seromuscular bites through the jejunum (Figure 1).

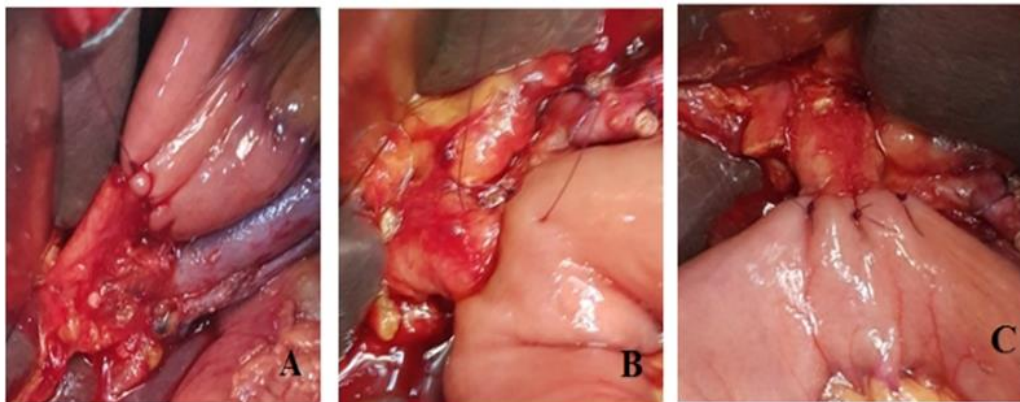


Fig. 1. Creation of straight hepaticojejunostomy (SA HJA): A) dorsal wall of the SA with interrupted extraverted sutures, B) suturing of the ventral wall of the anastomosis, seromuscular on the jejunum, and perforating on the common bile duct, C) completed SA HJA

In all 50 patients pancreaticojejunostomy (PJA) was performed in a same unified fashion, using invagination dunking anastomosis (DA) with placement of an internal stent. The remaining reconstruction was also standardized: a double-layer gastrojejunostomosis was performed on the anterior wall of the resected stomach, and a double-layer enteroenteroanastomosis was performed, providing a long-isolated diversion omega efferent loop. After completion of the surgery, 3 silicon tube drains were placed: one from the left in bursa omentalis-lesser sac, one in the subhepatic space, adjacent to the HJA, and one in the Douglas excavation.

Results

There were 40 male and 10 female patients, median age 62.68 ± 10.77 .

Postoperatively, we monitored several parameters defining the postoperative morbidity, including BF-biliary leakage, the onset or persistence of reflux cholangitis (RC) beyond the 5th postoperative day, appearance of clinically relevant POPF grade B or C, and the length of postoperative hospital stay.

The appearance of BF was generally identified by bile excretion through the right abdominal drain. BF was defined as the presence of bile in the drain, with a bilirubin concentration 3 times higher than the serum level, from the 3rd postoperative day. By comparing the bilirubin concentration in the bile obtained intraoperatively from the open CBD with the bilirubin concentration in the drain liquid, we were able to estimate the precise origin of the fistula in accordance with the calculated bilirubin concentration and $V(\text{ml})/24 \text{ h}$. In our study, clinical distinction between persistent BF as a solitary issue and simultaneously present POPF was

achieved by placement of 2 silicone tube drains in the upper abdomen. One drain, as described previously, was positioned in the right subhepatic-subanastomotic space to drain fluid in the vicinity of HJA. The second drain was on the left, in the lesser sack, adjacent to the pancreas to drain fluid merely originating from the vicinity of the pancreaticojejunostomosis.

The parameters used to assess the onset/persistence of reflux cholangitis (RC) were: clinical pain in the upper right abdomen, fever ($>38^{\circ}\text{C}$), elevated serum bilirubin levels, increased liver enzymes in the laboratory probes (ALT, AST, gGT suggestive of obstruction or stenosis of the anastomosis), and SGOT AND SGPT as indicators for liver necrosis, inflammatory marker (leukocyte count, CRP), and US findings. These parameters were monitored until the 5th postoperative day, as a breaking point, because majority of patients in the study had suffered preoperative RC, due to ERCP/PTC and stenting. The presence of these findings longer than 5 days postoperatively was considered indicative of onset/persistence of RC.

POPF was identified by a drain fluid amylase concentration greater than three times the serum amylase level on the third postoperative day, with no detectable bilirubin in the drain fluid.

This was enabled by sufficient separation of the PJA and HJA using a long efferent jejunal loop. Clinical assessment also included delayed gastric emptying, paresis, upper abdominal pain, prostration, and inflammatory markers such as leukocyte count and CRP.

The quality control throughout the study was ensured by a single surgical team.

During the study period, one patient developed BF, manifested by bile leakage through the right drain. BF was managed conservatively, without significant influence on postoperative morbidity, and the patient was discharged on the 17th postoperative day.

The second parameter analyzed was the onset/persistence of RC. In the entire group of 44 preoperatively confirmed cases with RC due to stenting via ERCP and PTC, 26 patients (59%) experienced postoperative persistence of RC longer than 5 days. These patients were treated with antibiotics according to antibiogram obtained intraoperatively, but it did not lead to prolonged hospital stay. One patient developed intrahepatic abscess, which was successfully managed with US-guided external drainage. In the remaining 18 patients, no signs of RC were observed after the 5th postoperative day.

Among patients in this study, 11 patients developed POPF grade B (Clavien Dindo grade II), while 6 POPF grade C (Clavien Dindo grade IIIa 2 patients and grade IIIb 4 patients) a total of 17 patients (34%). The mean postoperative hospital stay was 10.54 ± 6.20 days.

Perioperative mortality in our series occurred in 3 patients (6%). As previously notified, the cause of death was pulmonary embolism-one patient (no signs

of POPF), and two patients with grade C POPF, of whom one died from sepsis, while the other developed multiple system organ failure following postpancreatectomy hemorrhage (PPH). These 2 patients underwent reoperation; however, the outcomes were fatal.

Discussion

The majority of patients who underwent stenting of the CBD via ERCP/PTC (44 of 46), had a thickened, phlegmonous, and fragile wall of the CBD, accompanied by collapse and reduction in duct diameter. Purulent bile and bacterial infection was present in 95% of cases. On the other hand, 4 patients without stenting, were anicteric, without biliary obstruction and without stenting via ERCP. They had a narrow CBD (less than 4 mm), and a thin wall (less than 1 mm). This morphological status of the CBD was a consequence of the topographic location of the PHC in the uncinate process, distantly from the CBD, and these patients underwent HJA with a longitudinal incision of the CBD.

The surgical procedure was standardized throughout the study group. Thus, we avoided the influence of other factors adjacent to the procedure. However, the impact of local individual risk factors, such as a soft pancreas, a small caliber of the main pancreatic duct, operative site infection, preoperative cholangitis, and POPF, could not be completely eliminated.

Among the 50 patients included in the study, one patient developed BF. This complication is generally manageable and primarily affects postoperative morbidity if occurs as an isolated entity.

A large Italian study analyzing a series of 1,618 patients who underwent PD, reported 22 cases of simultaneous BF and POPF grade C. Such a concomitant presence of these two complications demonstrated a supra-additive synergism as a noxious effect, resulting in significantly increased mortality. Eight of the 22 patients (34.8%) died, a rate substantially higher than would be expected from either BF or POPF grade B and C alone [4]. A study evaluating BF as an isolated entity after hepatic surgery reported only 1 death from 74 patients, occurring three months later and unrelated to the preceding surgery [6]. Furthermore, the expected mortality associated with grade C POPF is approximately 25%, accompanied by severe complications, such as bleeding, intra-abdominal abscess, sepsis [7-9]. These data confirm the predicted supra-additive harmful contribution of these 2 independent entities, BF and POPF grade C if present simultaneously. Unfortunately, in our series, there were 3 deaths, 2 associated with POPF grade C, and one without any leakage, either biliary or pancreatic.

In our study, 44 from 46 stented patients had been treated for RC preoperatively. The incidence of persistent postoperative RC beyond postoperative day 5 was 26 from 44 patients (59%). The persistence of signs of

temporary stenosis was also frequent, occurring in 8 patients. In this study, postoperative onset/persistence of RC was consequence of preoperative stenting, which had been performed in 88% of the patients (44 of 50). Our results regarding onset/persistence of RC are generally comparable with other published studies [10]. It is also worth to mention that no patient developed long-term or persistent biliary obstruction due to stenosis of the HJA requiring invasive intervention or reoperation.

We can also discuss the preoperative treatment of RC and intraoperative preventive measures applied during the technique of HJA construction. Preoperatively diagnosed RC was treated with antibiotics according to antibiogram, and antibiotic therapy was continued postoperatively based on intraoperatively obtained material from the resected hepatic duct. The significantly decreased numbers of clinically present RC in our patients following surgery support the success of this management [11-13]. In addition, other factors, such as the length of the diversion efferent jejunal loop have been reported to play a prominent role in prevention of RC [14,15].

BF after biliary surgery develops in 3-8% of cases, and the incidence may depend on various risk factors, including preoperative radiochemotherapy and diabetes mellitus [4,16]. This procedure may occur independently or in association with PD and PJA. When PD is performed, and if POPF grade B or C develops, many surgeons consider POPF to be the primary event, with the erosive effect contributing to the development of secondary BF. In our cases, one BF emerged as an isolated complication without POPF. This BF was low outlet based on bilirubin concentration, and V/24 h. Clinically it corresponded to BF grade A, without significant influence on the patient's overall status [17]. The onset of BF in our study is similar to that reported in other tertiary surgical centers (2% vs. 3.6%). Furthermore, comparing the simultaneous presence of BF and POPF grade C in our series to other referral centers, it was 0% as opposed to an average of 38% reported in the literature. This difference may be due to the relatively small number of patients included in our study.

Many studies have emphasized that the crucial influence on the success and desired outcome of HJA depend on the surgical technique [4]. Since 1903, when Dahl first reported HJA, many modifications of the suturing technique have been developed. Nowadays, several suture techniques are being performed by surgeons: A) single-layer interrupted suture, B) single-layer continuous suture, C) combined technique using these two, dorsal wall continuous, ventral interrupted or inversely-dorsal layer interrupted and ventral continuous, and D) recently reported and promoted mechanical anastomosis using a circular mechanical stapling device.

The first three techniques of creating HJA are well known, and widely accepted by surgeons [18]. The

recently described mechanical anastomosis may be only performed in cases of marked dilatation of CBD [19]. In addition, creating the anastomosis close to the hepatic bifurcation may be helpful by providing a short duct with well blood supply and lower resistance to the bile flow [20]. The final decision for the choice of technique depends on the experience and judgement of the hepatobiliary pancreatic surgeon. The only alleged issue may be the use of continuous suture in a narrow CBD (less than 3 mm caliber) with a thin fragile wall.

According to the available literature regarding biliary leakage-BF, there is no superior technique for creation of HJA [18-20]. There is also a notable lack of data and trials investigating postoperative RC. Future large clinical trials may contribute to more precise criterion for selection of the suturing technique. However, considering the low incidence of postoperative persistence of RC, and all other adverse events of HJA, including the onset of postoperative BF, absence of long-term stenosis, this classical suturing technique appears to be feasible and safe.

The mean hospital stay in our study was 10.5 days, which is similar to that reported in other high-volume centers. Prolongation of the hospital stay mainly depended on the onset of clinically relevant POPF, and was not associated with BF. Thus, the patient who developed BF was treated conservatively and discharged on the 17th postoperative day.

As anticipated, reducing preoperative infection and RC lead to a lower incidence of postoperative onset/present RC, and consequently a shorter hospital stay. Therefore, avoiding preoperative stenting via ERCP and/or PTC and referring directly these patients to surgery may significantly reduce hospitalization and improve the cost-benefit ratio [21].

The mortality rate of PD has generally declined from 20% to less than 5% in some high-volume tertiary centers over the last 20 years, reaching less than 2%. This adverse outcome may be rather associated with the combined of BF and POPF grade C, as well as with other concomitant diseases, than with the presence of BF as an isolated condition. In our study, the mortality rate was 6%, which is comparable to that reported by other high-volume centers. Furthermore, mortality directly attributable to isolated BF in our study was 0%, similar to other trials [6]. Three patients (6%) died during the study period: one from pulmonary thromboembolism, and two from POPF grade C. These two patients underwent reoperation, and pancreatic anastomotic failure was converted to pancreatic occlusion failure. Unfortunately, the clinical course was fatal, with one patient dying from sepsis and the other from MOF [7,8,22].

Conclusions

So far, no clear and conclusive results from randomi-

zed clinical trials have demonstrated the superiority of any of these suturing techniques for the creation of HJA. The choice of the procedure largely depends on the surgeon's preference and experience, and is best performed in high-volume centers.

To obtain relevant data and avoid bias and ambiguity arising from other risk factors, future studies should include carefully selected and stratified patient groups that differ only in the suturing technique. Thus, to avoid the risk of onset of clinically relevant POPF, we suggest HJA without pancreatic surgery or undergoing total pancreatectomy. Separate studies should be conducted for patients who undergo stenting or PTC, and those who do not. Patients groups should also be stratified and balanced according to the presence of preoperatively diagnosed bacterial RC.

Finally, based on our results, we consider the described standard suturing technique for the creation of HJA in this study to be safe, feasible and beneficial. The only limitation of this technique may be related to local operative conditions.

Conflict of interests: None declared.

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