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Early combined parenteral and enteral nutrition for pancreaticoduodenectomy – Retrospective cohort analysis



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HIGHLIGHTS

- ECPEN is one possible nutritional technique after pancreaticoduodenectomy.
- The coverage of caloric requirements per patient was 93.4%.
- The coverage was higher in patients with needle catheter jejunostomy.
- With ECPEN malnutrition or immunonutrition did not affect outcomes.

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ABSTRACT

Background: Suggested guidelines for nutritional support after pancreaticoduodenectomy are still controversial. Recent evidence suggests that combining enteral nutrition (EN) with parenteral nutrition (PN) improves outcome. For ten years, patients have been treated with Early Combined Parenteral and Enteral Nutrition (ECPEN) after PD. The aim of this study was to report on rationale, safety, effectiveness and outcome associated with this method.

Methods: Consecutive PD performed between 2003 and 2012 were analyzed retrospectively. Early EN and PN was standardized and started immediately after surgery. EN was increased to 40 ml/h (1 kcal/ml) over 24 h, while PN was supplemented based on a daily energy target of 25 kcal/kg. Standard enteral and parenteral products were used.

Results: Sixty-nine patients were nutritionally supplemented according to ECPEN. The median coverage of kcal per patients related to the total caloric requirements during the entire hospitalization (nutrition balance) was 93.4% (range: 100%–69.3%). The nutritional balance in patients with needle catheter jejunostomy (NCJ) was significantly higher than in the group with nasojejun tube (97.1% vs. 91.6%; $p < 0.0001$). Mortality rate was 5.8%, while major complications (Clavien-Dindo 3–5) occurred in 21.7% of patients. Neither the presence of preoperative malnutrition nor the application of preoperative immunonutrition was associated with postoperative clinical outcome.

Conclusion: This is the first European study of ECPEN after PD. ECPEN is safe and, especially in combination with NCJ, provides comprehensive coverage of caloric requirements during the postoperative

Abbreviations: ABW, adjusted body weight; ASA, American Society of Anesthesiology; ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, body mass index; CVC, central venous catheter; DGE, delayed gastric emptying; DGEM, German Society for Nutritional Medicine; ERAS, Enhanced recovery after surgery; ECPEN, early combined parenteral and enteral nutrition; ICU, intensive care unit; IBW, ideal body weight; NCJ, Needle catheter jejunostomy; NRS, nutritional risk screening; PD, Pancreaticoduodenectomy; POPF, postoperative pancreatic fistula; RCT, randomized controlled trial.

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phase. Clinical controlled trials are needed to investigate potential benefits of complete energy supplementation during the early postoperative phase after PD.

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1. Introduction

Pancreaticoduodenectomy (PD) is the only potential curative approach to treat premalignant and malignant neoplasms of the pancreatic head [1,2]. Although the surgical procedure is widely standardized, guidelines about postoperative nutrition differ throughout the world. While the American Society for Parenteral and Enteral Nutrition (ASPEN) does not recommend any nutritional support when sufficient oral intake can be resumed within 7–10 days [3], the Society for Enhanced Recovery after Surgery (ERAS) suggests early oral intake (starting at the first day after surgery), which should be carefully increased over 3–4 days after pancreaticoduodenectomy [4]. As a further option, the German Society for Nutritional Medicine (DGEM) recently published guidelines based on a consensus which included experts from national nutritional societies from Switzerland and Austria. The DGEM recommends a supplementation with parenteral feeding, if less than 60% of daily caloric requirements can be achieved orally or enterally within 4 days [5].

In general, beneficial effects of postoperative oral or enteral nutrition (EN) compared to the parenteral route on energy intake in surgical patients are widely accepted [5]. However, delayed gastric emptying (up to 57%) and/or intestinal paralysis may lead to insufficient postoperative caloric intake, particularly after PD [6]. In order to compensate for deficiencies in postoperative caloric intake, the relevance of the application of additional parenteral nutrition (PN) as well as the impact of different routes of enteral supplementation (nasojejun tube or needle catheter jejunostomy (NCJ)) remain unclear.

A recent randomized controlled trial has shown that additional PN is safe and effective in critically ill patients in the intensive care unit (ICU) [7]. Focusing on patient collectives after PD, a few Asian studies confirmed beneficial effects of combined postoperative EN and PN as compared to either enteral [8] or parenteral [9] nutrition alone. Furthermore, a systemic review conducted in 2013 comparing five feeding routes after PD (oral, nasojejun tube, gastrojejunostomy tube, NCJ, and PN) favored oral postoperative feeding. However authors did exclude studies with combined PN and EN [10].

The primary objective of the present study was to analyze safety and effectiveness of early combined parenteral and enteral nutrition (ECPEN) after PD, and secondarily to assess the impact of different enteral routes (nasojejun tube versus NCJ) on total caloric intake and outcome.

2. Material and methods

This is a retrospective single cohort analysis. Consecutive patients receiving standardized ECPEN after PD were included in this retrospective outcome analysis. Patients with different nutritional regimens other than ECPEN were excluded. Operations were performed between 2003 and 2012 by three senior surgeons. This study was approved by the local ethics committee (KEK-ZH-Nr. 2013-0079) and is registered on [researchregistry.com](http://www.researchregistry.com) (researchregistry826).

2.1. Pre- and intraoperative standards

Pre- and intraoperative procedures were standardized among all included patients. Somatostatin was used in presence of a soft texture of the pancreas. Prior to 2007 patients did not receive any nutritional supplements before surgery. Since 2008 preoperative immunonutrition (including Omega 3 fatty acids, nucleotides and arginine) was applied routinely. Pylorus preserving PD followed by placement of a feeding tube was performed in all of the patients. The anastomosis of the pancreas was carried out as end to side pancreatojejunostomy with resorbable suture material.

2.2. Postoperative early combined parenteral and enteral nutrition (ECPEN)

ECPEN was started immediately after transfer to the ICU. EN started with 20 ml/h (1 kcal/ml) and was increased by 5 ml/h every six hours to a maximum of 40 ml/h. Additionally, PN was supplemented to cover total daily caloric requirement.

Daily caloric requirement was defined as 25 kcal/kg of ideal body weight (IBW; Males: $IBW (kg) = 50.0 kg + 2.3 kg$ for every 2.54 cm taller than 152.4 cm; Females: $IBW (kg) = 45.5 kg + 2.3 kg$ for every 2.54 cm taller than 152.4 cm) [11,12]. If the actual body weight was >30% greater than the IBW, adjusted body weight (ABW; $ABW (kg) = IBW + 0.4 \times (actual\ weight - IBW)$) was used to calculate daily caloric needs [13]. From 2003 to 2008, EN was applied via a nasojejun tube; between 2009 and 2012, a NCJ was placed into the jejunum 20 cm from the Treitz ligament. PN was applied via a central venous catheter (CVC). For both EN and PN, standardized products with supplements of vitamins, minerals, and trace elements were used, covering daily requirements. No immunonutrition was used postoperatively.

Oral fluid intake after PD was initiated at the earliest 6 h after surgery depending on the occurrence of nausea, awareness and pain. Oral food intake was started, if bowel sounds were detectable. Further increase of food intake was based on gastrointestinal function.

Nursing personnel documented daily amounts of caloric intake by oral, enteral, and parenteral routes. As soon as the oral intake of calories increased, PN and then EN were decreased, respecting the total daily requirements of calories (25 kcal/kg of IBW or ABW per day) during the whole hospitalization [11]. The caloric value of oral intake was calculated based on nutritional standards of the institution (fluid nutrition between 675 kcal/d and 1150 kcal/d, stuffed nutrition 1000 kcal/d, solid nutrition 1700 kcal/d).

A control of serum glucose concentration (target serum glucose < 8 mmol/l) was granted to prevent hyperglycemia [14]. Patients were transferred to the ward as soon as they were considered to be hemodynamically stable and fit enough for off bed physiotherapy. Subsequently, daily medical consultation and nutrition counseling were performed. In case of chylous ascites, EN was stopped for a minimum of 3 days and replaced by total PN [15].

2.3. Outcome parameters

The primary outcome parameter was the caloric intake by ECPEN. Therefore, the nutritional balance representing the

coverage of kcal per patients related to the total caloric requirements during the entire hospitalization was calculated. The maximum possible coverage was 100% and over-coverage was not taken into account for calculating means and medians. Additionally, the number of days with 100% coverage of daily caloric requirements during the catabolic stress period of seven days [16] compared to the entire postoperative hospitalization time were analyzed. In order to prevent confounding, in cases of complications, caloric balances of days with re-interventions were not taken into account.

As a secondary endpoint postoperative complications according to the Clavien-Dindo classification were assessed [17]. Minor complications were defined as grade 1 and 2, while major complications were summarized between grades 3–5. Validated, pancreas-specific complications such as delayed gastric emptying (DGE), postoperative pancreatic fistula (POPF) and post-pancreatectomy hemorrhage (PPH) were recorded separately [6,18,19].

Finally, the impact of different routes for enteral feeding (nasojejun tube versus NCJ), in terms of attaining the recommended daily caloric intake, the effects of preoperative immunonutrition and the presence of malnutrition [20] on outcome, were assessed.

2.4. Statistics

Statistical analysis was performed with R (version 3.1.1) [21]. Chi-square or Wilcoxon rank sum test were used as appropriate. Level of significance was set at $\alpha < 5\%$. Exact p-values were calculated for reliable interpretation. All analysis had an exploratory character without the purpose to confirm a hypothesis.

3. Results

Seventy-five patients operated on between 2003 and 2012 for PD were assessed for eligibility. Sixty-nine patients were treated according to ECPEN. Six patients had oral nutritional support only and were therefore excluded from analysis. Baseline characteristics are shown in Table 1. The median age of patients was 68 years, while BMI ranged from 19.4 kg/m² to 37.8 kg/m². In 39.1% of the patients ASA score was 3 or 4. From a nutritional point of view, 82.6% of the patients were at risk with a Nutritional Risk Score (NRS) ≥ 3 [20]. Decreased food intake, rather than weight loss or low BMI, was the main cause for additional points in the NRS-Score. Three patients suffered from systemic inflammatory response syndrome at the time of operation with a NRS of 6 or 7 points. Regarding intraoperative parameters, 50.7% of the patients received nasojejun tube (between 2002 and 2007), while in 49.3% of the cases (between 2008 and 2012) a NCJ was installed.

The primary endpoint of this study, the median nutritional balance (coverage of calories per patient related the energy requirements during hospitalization) of the whole collective was 93.4% (range: 100%–69.3%), which represents an average deficit of 754 kcal (range: 0–16350 kcal) per patient over the whole hospitalization (Fig. 1). Complete caloric intake of 25 kcal/kg/d was achieved in 1081 out of 1516 patient days (71.3%). Analyzing the most intense catabolic stress period of the first 7 days, caloric requirements were covered in 6 out of 7 days (Table 2).

Postoperative outcomes are shown in Table 3. Four patients (5.8%) died postoperatively. Reasons for mortality were septic shock in three patients and multi organ failure initiated by a portal vein thrombosis in one patient. The rate of major complications was 21.7% (15 out of 69). DGE occurred in 13 patients (18.8%), whereas two had to undergo endoscopic decompression (2.9%). The other 11 patients were treated conservatively (metoclopramide, erythromycin). The fistula rate of pancreatic anastomosis was 15.9% (grade

Table 1
Baseline characteristics and intraoperative parameters.

	Patients n = 69
Gender (n)	
Male	49 (71.0%)
Female	20 (29.0%)
Age (y) ^a	68 (39–88)
BMI (kg/m ²) ^a	24.4 (19.4–37.8)
ASA Class (n)	
1	5 (7.2%)
2	37 (53.7%)
3	25 (36.2%)
4	2 (2.9%)
NRS Score (n)	
2	12 (17.4%)
3	18 (26.1%)
4	21 (30.4%)
5	15 (21.8%)
6	2 (2.9%)
7	1 (1.4%)
Cause of surgery (n)	
Pancreatic cancer	38 (55.1%)
Papillary tumor	10 (14.5%)
IPMN	5 (7.2%)
Cholangiocarcinoma	4 (5.8%)
Neuroendocrine tumor	4 (5.8%)
Chronic pancreatitis	3 (4.4%)
Other	5 (7.2%)
Operative time (min) ^a	450 (182–820)
Peoperative Immunonutrition (n)	35 (50.7%)
Postoperative Enteral feeding (n)	
Nasojejun tube	35 (50.7%)
Needle catheter jejunostomy	34 (49.3%)

^a Median with range; ASA: American society of anesthesiology; NRS: Nutritional risk screening; IPMN: Intraductal papillary mucinos neoplasm.

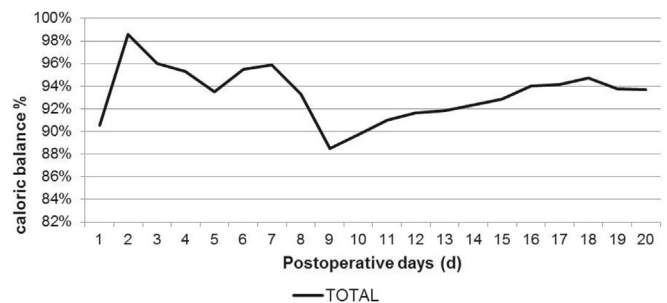


Fig. 1. Postoperative caloric balance.

A: 0, grade B: 7, grade C: 4). One patient developed an additional bile leak grade C (1.4%). No PPH was observed. The mean length of hospital stay was 23.2 days, with a mean of 6.8 days in the ICU. The first bowel movement was observed on postoperative day 5. More than 50% of the patients were discharged directly to their homes.

Regarding feeding routes, the nutritional balance in patients with NCJ was significantly higher than in the group with nasojejun tube (97.1% vs. 91.6%; $p < 0.0001$; Fig. 2). Major complications did not differ between patients with NCJ or nasojejun tubes (22.9% vs 20.6%; $p = 0.5192$). However, one small bowel resection due to a jejunal fistula, which was related to an NCJ, (1.4%) had to be performed. Neither the application of preoperative immunonutrition nor the occurrence of preoperative malnutrition (NRS ≥ 3) was significantly associated with clinical outcome (Table 4).

4. Discussion

ESPEN after PD is safe and allows for optimized caloric intake

Table 2
Caloric intake.

Nutritional balance (%) ^a	93.4% (100–69.3%)
Individual caloric deficit during hospitalization(kcal) ^b	754 (0–16350)
25 kcal/kg achieved during hospitalization (overall days)	1081/1516 (71.3%)
25 kcal/kg achieved during first seven postoperative days ^a	6 (0–7)

Nutritional balance: the % coverage of kcal per patients related to the total caloric requirements during the entire hospitalization.

^a Median with range.
^b Mean with range.

Table 3
Perioperative outcomes.

	Patients n = 69
Mortality	4 (5.8%)
Morbidity (Clavien-Dindo)	
None (0)	15 (21.7%)
Minor (1 + 2)	39 (56.6%)
Major (3–5)	15 (21.7%)
DGE (n)	
A	11 (15.9%)
B	2 (2.9%)
C	0 (0%)
POPF (n)	
A	0 (0%)
B	7 (10.1%)
C	4 (5.8%)
PPH (n)	0 (0%)
LOS (d) ^a	23.2(±11.6)
ICU (d) ^a	6.8 (±4.6)
Place of discharge (n)	
Home	38 (55.1%)
Health resort	7 (10.1%)
Rehabilitation facility	19 (27.6%)
Death	4 (5.8%)
Internal medicine	1 (1.4%)
First bowel movement (d) ^a	5.6 (±2.8)
CVC removed (d) ^a	10 (±4.7)

DGE: delayed gastric emptying; POPF: postoperative pancreatic fistula; PPH: postpancreatectomy hemorrhage; LOS: length of stay; ICU: intensive care unit; CVC: central venous catheter.

^a Mean with standard deviation.

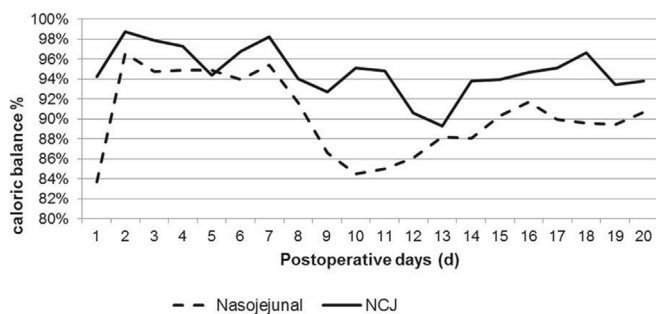


Fig. 2. Postoperative comparison of caloric balance between feeding routes.

with regard to individual daily postoperative energy requirements. The installation of a NCJ reduces postoperative caloric deficits to a minimum.

The optimal route and timing for nutritional support after PD is under debate [22]. While the paradigm of preoperative fasting of patients is outdated [23], early oral postoperative food intake within fast-track pathways such as the ERAS concept [4] gain evidence and interest. A recent publication in ICU patients confirms the negative impact of postoperative caloric deficit on the occurrence of postoperative complications [24]. This finding contradicts

Table 4
Rate of complication in subgroup analyses.

Yes	Immunonutrition Complication	No	p
7 (20.0%)	None	8 (23.5%)	p = 0.7125
19 (54.3%)	Minor	20 (58.9%)	
9 (25.7%)	Major	6 (17.6%)	
<3	NRS		p = 0.3486
4 (33.3%)	Complication	≥3	
7 (58.4%)	None	11 (19.3%)	
1 (8.3%)	Minor	32 (56.1%)	p = 0.5192
	Major	14 (24.6%)	
	Feeding route		
NCJ	Complication	Nasojejunal	p = 0.5192
8 (22.9%)	None	7 (20.6%)	
19 (54.2%)	Minor	20 (58.8%)	
8 (22.9%)	Major	7 (20.6%)	

previous opinions, that postoperative caloric deficits after major surgery have to be accepted as “physiological adaption of the metabolisms” with reduced requirements of caloric intake, particularly in the early postoperative phase [5]. However, there is a lack of scientific evidence on this topic. Most guidelines are based on consensus of experts regarding timing and extent of postoperative nutritional care following specific procedures such as PD [3,5].

Based on the intent to optimize clinical outcome by covering a maximum of caloric requirements postoperatively, the strategy of ECPEN was initiated. The two aspects which were considered were the early postoperative start of the nutritional support and the combined enteral and parenteral route of nutritional support. The rationale behind the addition of PN to the enteral intake was to reduce the risks of paralysis and of non-occlusive mesenteric ischemia, by limiting the amount of high caloric fluids introduced into the bowel [25].

After two comparative trials in Asiatic populations, in 17 and 174 [8,9] patients respectively, the present cohort represents the first study in Europe to evaluate the effect of ECPEN after PD. In addition to postoperative nutritional care, surgical as well as postoperative procedures were highly standardized. Only 3 senior pancreatic surgeons performed the operations.

The present data confirms that ECPEN is a possible method to optimize caloric intake after PD. Complete intake of daily caloric requirements by ECPEN was reached in 6 out of 7 days while caloric balance was 93,4% over the whole hospitalization. In comparison, other strategies of postoperative nutritional support include a slow increase of postoperative caloric intake leading to an obviously lower caloric balance after PD.

The mortality rate of 5.8% and the occurrence of 21.7% major complications after PD with standardized ECPEN in the present collective are in line with expected outcome data after PD for non-high volume centers [26]. A trend indicating that patients with less caloric deficit had fewer major complications was also observed. However, this study is certainly underpowered. Specific complications such as DGE (18.8%) and POPF (15.9%) were low in relation to the expected range of occurrence (DGE 0–45% and POPF 6–38%).

However, the fact that no POPF grade A was identified has to be considered carefully since the outcome data was collected retrospectively. In this context the identification of minor events without further therapeutic consequences is more challenging [26,27]. Nevertheless, the outcome after ECPN is encouraging, particularly with regard to rehabilitation and overall cost of health care, since more than 50% of the patients could be discharged directly to their homes.

This study's data supports evidence that considering the whole hospitalization a higher caloric intake can be achieved by the use of an NCJ, rather than a nasojejun tube. Nasojejun tubes frequently required removal due to disturbance of the patient's facial-oral tract, thus resulting in a higher caloric deficit among those patients. In both groups CVC was withdrawn on postoperative day 8 and caloric intake decreased, since oral nutrition was generally insufficient. Although a continuous enteral supplementation by NCJ prevented a nutritional deficit in the present collective, the occurrence of postoperative complications was not significantly different (Table 4). One jejunal fistula related to NCJ occurred, which could be treated conservatively. Yet, with regard to the literature, the insertion of NCJ is correlated with a relevant risk for complications such as mechanical ileus [28,29].

The majority (57 patients, 82.6%) of patients requiring pancreatic surgery in the present cohort were malnourished with a NRS of ≥ 3 . Such high incidences of patients at nutritional risk prior to surgery have been confirmed in several other collectives including oncological patients. However, in contrast to the literature [30], in a subgroup analysis no significant difference was shown between malnourished and well-nourished patients with regard to the occurrence of postoperative complications, possibly indicating, that nutritional therapy of the malnourished patients led to same outcome (Table 4). Another fact was, that no correlation could be identified between the application of preoperative immunonutrition and postoperative complications (Table 4) [31,32]. Based on nutritional guidelines after 2009 [4,5], in order to improve postoperative outcome, immunonutrition was prescribed consecutively to 35 patients (50.7%) prior to pancreatic surgery in the present collective. However, the interpretation of subgroup analyses requires caution.

The retrospective, single cohort design in a non-high volume center is the obvious limitation of the present study and has to be considered for interpretation of the results. Moreover, the statistical power was not sufficient for final interpretation of non-significant differences within subgroups and was solely exploratory. On the other side, some results of this presented ECPN concept are promising. One could speculate that benefits of this therapeutic strategy might compensate for preoperative predicting factors such as malnutrition or the application of immunonutrition. However, with the presented study design no causal relationship between the applied nutritional technique and outcome can be confirmed. Therefore, the only purpose of this study was to share our experience with the applied nutritional technique and generate hypothesis for further investigation of the impact of the ECPN strategy, which aims to optimize caloric intake in the early postoperative phases.

In conclusion this is the first trial on ECPEN after PD in Europe. ECPEN is safe and, especially for patients with an NCJ, provides comprehensive coverage of nutritional needs during the postoperative phase. Further investigation is required to investigate potential benefit of ECPEN in comparison to other strategies of perioperative nutritional support.

Competing interests

None of the author has a conflict of interest according to the

ICMJE guidelines.

Authors' contributions

PP designed the study, analyzed data and drafted the manuscript. DK and JS acquired data and drafted the manuscript. EG analyzed and interpreted data and drafted the manuscript. AH, RI, MR and HG analyzed and interpreted data and revised the manuscript critically. SB designed the study, analyzed data and drafted the manuscript. All authors gave their final approval of the version to be published and agreed to be accountable for all aspects of the work.

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