

# Nutritional Support after Open Liver Resection: A Systematic Review

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## Key Words

Nutrition, perioperative · Liver function · Hepatic resection, partial · Enteral nutrition, total · Parenteral nutrition

## Abstract

**Background:** Perioperative nutrition in patients with limited liver function after partial hepatic resection is still controversial. In particular, the significance of perioperative total enteral nutrition remains unresolved. The aim of this review is to investigate the impact of early postoperative total enteral nutrition on convalescence after partial liver resection. **Materials and Methods:** In an internet-based Medline-Search (time course: 1960–08/2005) a total of five prospective, randomized controlled trials were found comparing the impact of enteral and parenteral nutrition after liver resection. After study validity had been established, a systematic review was undertaken (odds ratio, 95% confidence interval,  $p < 0.05$  level of significance; Review Manager 4.2®, The Cochrane Collaboration). Primary endpoints were complication rate (infection, organ malfunction) and mortality. Standardized immune parameters were also surveyed. **Results:** Statistical analysis showed that enteral nutrition resulted in a significantly lower rate ( $p = 0.04$ ) of wound infection and catheter-related complications than parenteral nutrition did. No statistically significant differences in mortality due to enteral or parenteral nutrition could be found. Patients receiving enteral nutrition showed better postoperative immune competence. **Conclusion:** Early enteral nutrition after liver resec-

tion is a safe procedure. Compared to parenteral nutrition it is associated with a decreased incidence of postoperative complications. Facing the inhomogeneity of these trials, especially in nutrition protocols and end points, this first systematic review stresses the need for an update of the importance of early enteral nutrition after liver resection within randomized controlled multicenter trials.

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## Introduction

Catabolic processes often overshadow the postoperative metabolic state. The post-aggression syndrome is characterized by an endocrine imbalance with glucose intolerance and peripheral resistance to insulin, which can result in persistent hyperglycemic states with increased lipolysis and progressive proteolysis. Complications such as infection or multi-organ dysfunction may be the result. Recent basic and clinical research has shown convincing physiologic benefits of early enteral feeding in trauma patients [1–4].

During the last decade perioperative nutrition has been transformed from a tool to provide calorie and nitrogen support to a therapeutic device aimed at boosting the immune system and enhancing resistance to complications. Surgeons have become more aware of the fact that early enteral nutrition (EN) prevents gastrointestinal atrophy, maintains immunocompetence and preserves

**Table 1.** Results (minor/major complications, mortality) of the studies comparing enteral and parenteral nutrition after liver resection

| Study                      | Complications |                          |            |             |             |                          | Mortality  |                        |
|----------------------------|---------------|--------------------------|------------|-------------|-------------|--------------------------|------------|------------------------|
|                            | total         |                          | minor      |             | major       |                          | EN         | PN                     |
|                            | EN            | PN                       | EN         | PN          | EN          | PN                       |            |                        |
| Shirabe et al. [7], 1997   | 1/13 (8%)     | 6/13 (46%)               | 0/13 (0%)  | 3/13 (23%)  | 1/13 (8%)   | 3/13 (23%)               | 0          | 0                      |
| Mochizuki et al. [8], 2000 | 13/24 (54%)   | 28/35 (80%) <sup>a</sup> | 8/24 (33%) | 19/35 (54%) | 5/24 (21%)  | 9/35 (26%)               | 0          | 0                      |
| Fan et al. [11], 1994      | 33/69 (55%)   | 22/64 (34%) <sup>b</sup> | 8/60 (13%) | 4/64 (6%)   | 25/60 (42%) | 18/64 (28%) <sup>c</sup> | 9/60 (15%) | 5/64 (8%) <sup>d</sup> |

Minor complications: catheter-associated infections and wound infection; major complications: pneumonia and abscess.

EN = Enteral nutrition; PN = parenteral nutrition.

<sup>a</sup> p = 0.02 vs. EN; <sup>b</sup> p = 0.02 vs. EN; <sup>c</sup> p = 0.01 vs. EN; <sup>d</sup> p = 0.3 vs. EN.

**Table 2.** Patients' characteristics in the studies comparing enteral and parental nutrition after liver resection

| Study                       | Number |    | Age, years (range) |            | Sex, male/female, n (%) |            |
|-----------------------------|--------|----|--------------------|------------|-------------------------|------------|
|                             | EN     | PN | EN                 | PN         | EN                      | PN         |
| Shirabe et al. [7], 1997    | 13     | 13 | 63 ± 11            | 60 ± 11    | n.d.                    | n.d.       |
| Mochizuki et al. [8], 2000  | 24     | 35 | 59 ± 8             | 60 ± 12    | n.d.                    | n.d.       |
| Hu and Zheng [9], 2003      | 65     | 40 | 60 ± 11            | 65 ± 9     | n.d.                    | n.d.       |
| Nishizaki et al. [10], 1997 | 10     | 9  | 62 ± 6             | 61 ± 8     | 7/10 (78)               | 8/9 (80)   |
| Fan et al. [11], 1994       | 60     | 64 | 54 (28–72)         | 53 (33–79) | 53/60 (88)              | 56/64 (88) |

EN = Enteral nutrition; PN = parenteral nutrition; n.d. = not determined.

the normal gut flora when compared to complete parenteral nutrition (PN) [5, 6].

The importance of early perioperative EN in patients with limited liver function, who require partial hepatic resection due to malignancy (e.g. hepatocellular carcinoma, cholangiocellular carcinoma and hepatic metastasis), has not yet been established. These patients often suffer from mild to severe malnutrition, making them more susceptible to disturbed metabolic homeostasis.

The available prospective, randomized controlled trials describe the impact of early EN after liver resection on the postoperative complication rate, mortality and metabolism. In themselves, they are unable to establish whether clinical outcome by maintaining gut function and immunocompetence is improved. The aim of this review is to compile existing studies and assess the impact of early EN after liver resection on postoperative convalescence.

## Materials and Methods

In an internet-based Medline-Search (time course 1960–08/2005, search terms 'parenteral nutrition', 'liver resection') five prospective, randomized controlled trials were found comparing the impact of EN and PN after liver resection. The retrospective studies were comparable with respect to the endpoints chosen [7–11]. No trials other than these five have been found. No hand search has been performed (library, congress literature, etc.). All studies included analyzed postoperative mortality, and in three studies the complication rate was the primary endpoint (infection, organ dysfunction; table 1). Some of the studies also surveyed immune competence and standardized anthropometric parameters such as grip strength, triceps skin-fold thickness and mid-arm circumference [9, 11]. The five studies encompassed 333 patients, 161 were randomized to receive PN and 172 to receive early EN. The patients' characteristics were comparable (table 2). All studies included patients with hepatic malignancies (hepatocellular carcinoma, cholangiocellular carcinoma, hepatic metastasis) for the most part with restricted hepatic function (Child-Pugh B, C). All patients received elective liver resection. Only one study compared the two nutritional protocols related to the extent of hepatectomy in compromised liver function [11].

In the studies EN was started for the most part on the 2nd postoperative day via an intraoperatively placed jejunal catheter, accompanied by electrolytes and hypocaloric infusion. Overall commercial EN solutions corresponding to hepatic and kidney function were administered.

PN was started via an intraoperatively placed central venous catheter immediately after operation and slowly increased to 30 kcal/kg/day within the first 3 postoperative days. This regime was continued to postoperative day 7, when EN was started [7–11].

#### Statistical Methods

After study validity was established according to the principles of evidence-based medicine, a systematic review was performed in five randomized studies comparing PN and EN following liver resection (OR <1 indicating a positive effect of the EN, 95% CI  $p < 0.05$  niveau of significance; Review Manager 4.2®, Cochrane Collaboration). End points were complication rate, incidence of infection, and mortality. Comparisons relating to the extent of the resected liver parenchyma and standardized anthropometric parameters such as grip strength, triceps skin-fold thickness and mid-arm circumference could not be included in the analysis due to the limited data.

## Results

Five prospective, randomized controlled trials were found comparing the impact of EN and PN after liver resection.

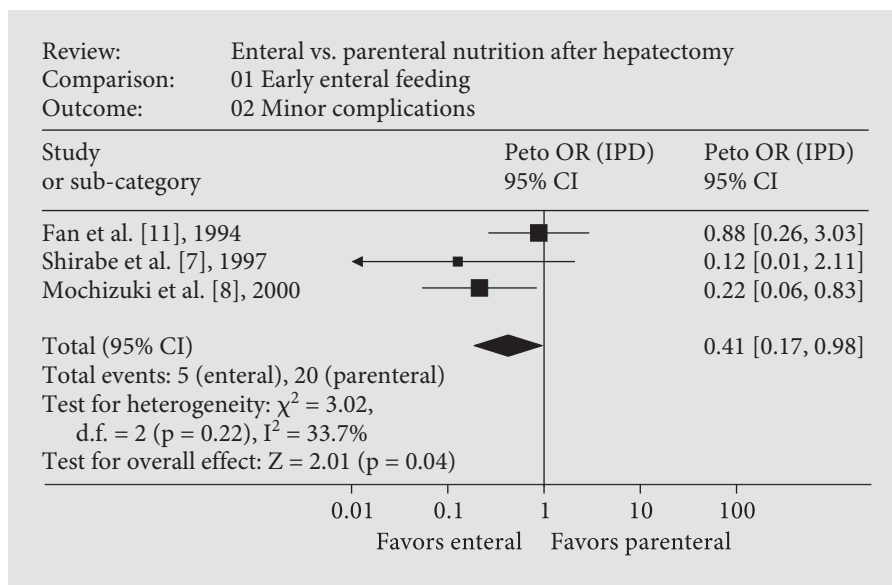
In the study by Shirabe et al. [7] no differences were found in the metabolic parameters (retinal-binding protein, transferrin, prealbumin, or 3-methylhistidine), but significant differences were found in immunological data: number of lymphocytes per cubic millimeter (EN vs. PN: 114 vs. 66,  $p < 0.05$ ), response to phytohemagglutinin (103 vs. 78% of preoperative values,  $p < 0.05$ ), and natural killer cell activity (106 vs. 49% of preoperative values,  $p < 0.05$ ). EN resulted in a lower complication rate than PN. While this study [7] failed to reach significance (EN vs. PN: 1/13 vs. 6/13), the study by Moshizuki et al. [8] resulted in a significantly decreased complication rate of EN (54 vs. 80%,  $p < 0.02$ ; table 1). Mortality was nil in both groups. Metabolic parameters and anthropometric data were not analyzed. Hu and Zheng [9] investigated the impact of nutritional support after liver resection among patients with poor liver function (Child-Pugh B, C). They found no impact on liver and kidney parameters. Initially, EN resulted in a positive nitrogen balance and a reduced loss of body weight. Furthermore, EN resulted in a preserved gut barrier as demonstrated by the lactulose/mannitol ratio. The complication rate was not determined and mortality did not occur in either group.

Nishizaki et al. [10] compared hypertonic PN and EN with supportive glucose infusions. In EN, the non-protein caloric intake was 20 kcal/kg/day, and in the PN group 30 kcal/kg/day. Again, no remarks on the overall complication rate were made and zero mortality was reported. PN resulted in increased plasma levels of retinal-binding protein ( $p < 0.05$ ) and prealbumin ( $p < 0.05$ ) as well as a significantly decreased urinary 3-methylhistidine excretion ( $p < 0.01$ ) and an earlier normalized nitrogen balance ( $p < 0.05$ ).

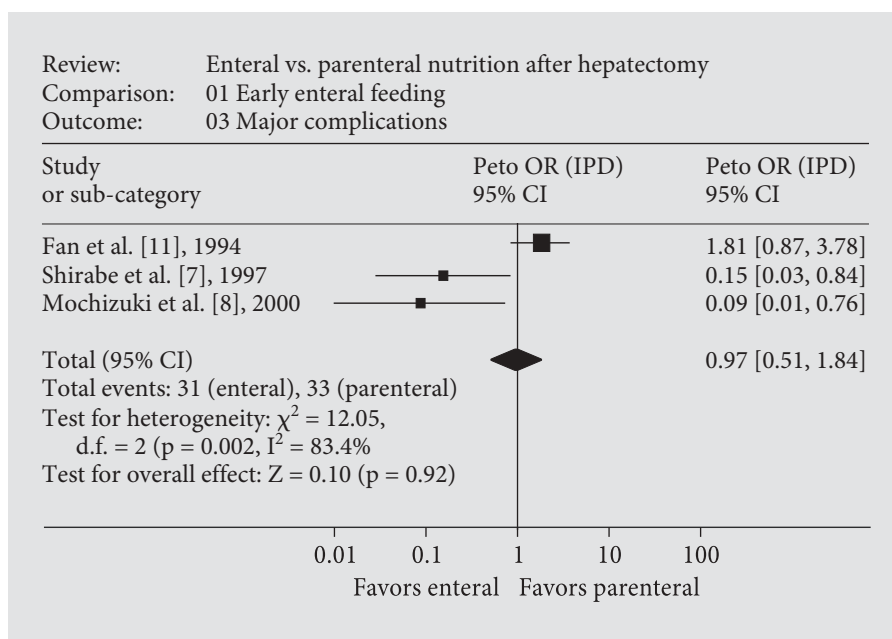
Finally, in the study by Fan et al. [11], PN was started 7 days before partial hepatectomy and continued until the 7th postoperative day. In the EN group postoperative enteral intake was to start as soon as possible, but was not clearly defined. The anthropometric data showed no differences between EN and PN. Liver function expressed by metabolic parameters was less compromised following PN as was the change in indocyanine green clearance (PN vs. EN:  $-2.8$  vs.  $-4.8\%$  at 20 min,  $p = 0.05$ ). The benefits of PN were predominantly seen in patients with underlying cirrhosis who underwent major hepatectomy. Nevertheless, patients with normal preoperative liver function undergoing major hepatectomy demonstrated a significant reduction in hospital morbidity with PN. In contrast, patients with minor hepatectomy (subsegmentectomy) or those with underlying chronic active hepatitis without cirrhosis did not benefit from PN. PN resulted in a reduced overall postoperative complication rate (34 vs. 55%), predominantly resulting from fewer septic complications and a lower mortality (8 vs. 15%; table 1).

In two of the studies [7, 8], EN tended to be associated with fewer minor complications (0 vs. 23% and 33 vs. 54%; table 1) while they were increased in another (13 vs. 6%; table 1) [11]. In summary, an OR of 0.41 (95% CI 0.17–0.98,  $p = 0.04$ ; fig. 1) shows that EN resulted in a significantly lower rate of wound infections and catheter-related complications than the PN group. As shown by minor complications, in two studies EN reduced the rate of major complications (EN vs. PN: 8 vs. 23% and 21 vs. 26%; table 1) [7, 8], while one study showed an increased major complication rate following EN (42 vs. 28%,  $p = 0.01$ ; table 1) [11]. In summary, with an OR of 0.97 (95% CI 0.51–1.84,  $p = 0.92$ ; fig. 2), EN was not associated with an increased rate of major complications.

When minor and major complications were summarized (total complication rate), the picture favored EN [7, 8] in two studies (8 [EN] vs. 46%, n.s.; 54% [EN] vs. 80%;  $p = 0.02$ ; table 1) while it showed a higher complication



**Fig. 1.** Minor complications (e.g. catheter-associated infection, wound infection) of parenteral and enteral nutrition after liver resection (Forest-Plot, Review Manager®, Cochrane Collaboration).



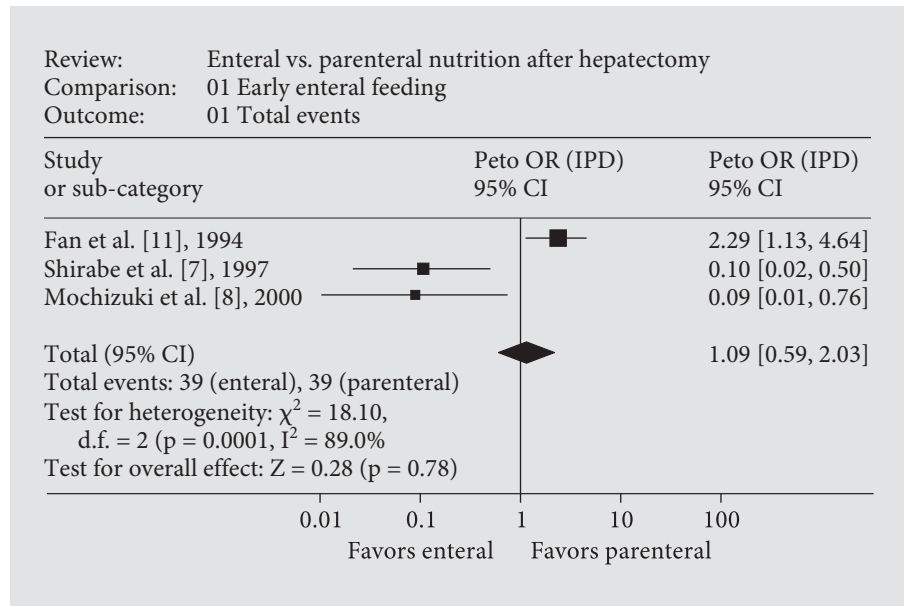
**Fig. 2.** Major complications (e.g. pneumonia, abscess) of parenteral and enteral nutrition after liver resection (Forest-Plot, Review Manager®, Cochrane Collaboration).

rate in another (55 [EN] vs. 34%, p = 0.02; table 1) [11]. In summary, an OR of 1.09 [95% CI: 0.59–2.03, p = 0.78] showed no superiority for either form of nutrition (fig. 3).

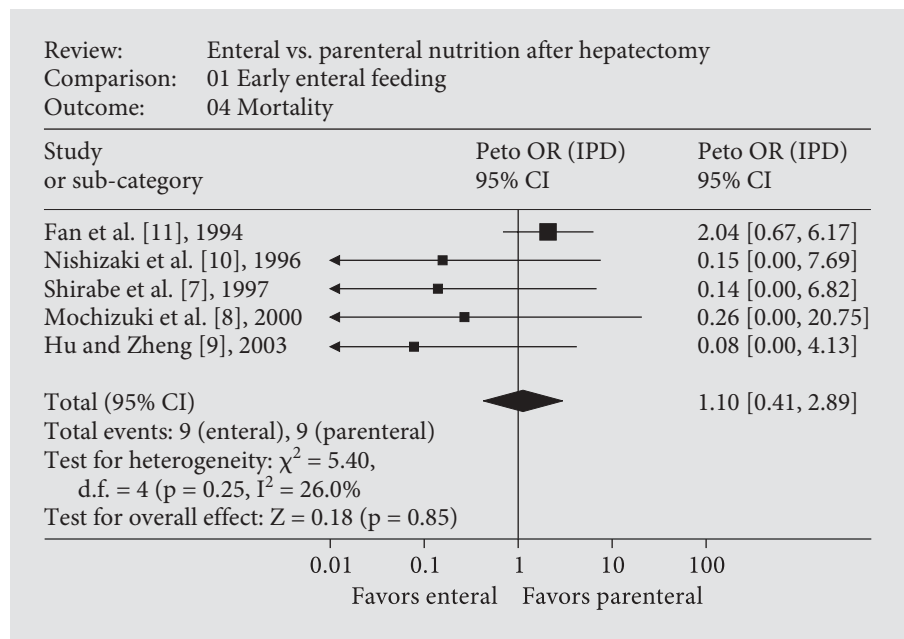
As shown in table 1, in four of the five trials no mortality was found [7–10]. One study registered an increased rate of mortality following EN (15 vs. 8%, n.s.;

p = 0.3; table 1) [11]. In summary, an OR of 1.1 (95% CI 0.41–2.89, p = 0.85) suggested no difference in mortality whether EN or PN was administered after liver resection (fig. 4).

Only one study focused on the extent of hepatectomy along with different stages of liver cirrhosis on the post-operative outcome [11]. A more detailed look into the



**Fig. 3.** Total complication rate of parenteral and enteral nutrition after liver resection (Forest-Plot, Review Manager®, Cochrane Collaboration).



**Fig. 4.** Mortality (e.g. pneumonia, abscess) of parenteral and enteral nutrition after liver resection (Forest-Plot, Review Manager®, Cochrane Collaboration).

subgroups showed that the benefits of PN were seen predominately in patients undergoing major hepatectomy (lobectomy, extended lobectomy) with or without liver dysfunction. On the other hand, patients with minor hepatectomy (subsegmentectomy) or those with underlying chronic active hepatitis without cirrhosis benefited from EN.

## Discussion

In 1991, Moore et al. [4] published their two-part meta-analysis (EN 118 patients, PN 112 patients) based on eight prospective randomized trials emphasizing a significantly reduced rate of septic complications in high-risk surgical patients following EN (18.5 vs. 35%). The most sig-



nificant difference was seen in trauma and blunt trauma subgroups [4]. Kudsk et al. [5] showed that less pneumonia (12 vs. 31%,  $p < 0.02$ ) and fewer abdominal abscesses (2 vs. 13%,  $p < 0.04$ ) were seen after blunt and penetrating abdominal trauma when EN was started within 24 h of the injury. Again, these differences were most apparent in more severe stages [5].

Following liver resection the studies included were not able to establish a definitive advantage of EN or PN. However, EN decreased minor complications (catheter-associated infection, wound infection) and one study investigating the impact of a fiber-enriched diet found an improved gut barrier and anthropometric parameters, as well as earlier normalized and stable metabolic parameters (liver and kidney function) [9]. Fan et al. [11] illustrated a potential link of EN and PN to the extent of hepatectomy and different stages of liver cirrhosis on postoperative outcome. The small amount of data made further statistical analysis within this review impossible. Their study [11] was somewhat contradictory to the other four trials emphasizing an increase in mortality and major complications in EN. The benefits of PN were predominately seen in a high-risk group with underlying cirrhosis undergoing major hepatectomy (lobectomy, extended lobectomy). While patients with minor hepatectomy (subsegmentectomy) or those with underlying chronic active hepatitis without cirrhosis benefited from EN. It is debatable whether the differing nutritional protocol design may have influenced the results. The EN group started postoperatively as soon as possible, with the 'patient being oriented'. Oral feeding was paralleled by supportive infusion (dextrose 5%, normal saline). In the PN group the nutrition protocol started 7 days prior to the operation and was continued until the 7th postoperative day. On the 8th postoperative day EN was started. The PN scheme was chosen to provide non-stop perioperative nutrition employing a normal calorie and protein content composition. Whether this regime can be applied to other health care systems is questionable.

Basic and clinical research underlines the importance of early EN by preserving the immunological competence of the gastrointestinal tract [1–4]. EN prevents gastrointestinal atrophy and preserves the normal gut flora. Both aspects are linked to the production of immunoglobulin A by the gut, known to prevent translocation, which is drastically reduced during mucosal atrophy [5, 6]. Data on immunocompetence after liver resection with EN or PN are somewhat inconsistent, showing a significantly depressed immune function [7] and also indifferent serum immunoglobulins and phytohemagglutinin

following PN [11]. EN and PN did not significantly alter anthropometric parameters. Nevertheless, in accordance with the published results [1–6, 12–15], early enteral feeding is likely to maintain intestinal and systemic immunocompetence and thus may contribute to a reduced rate of infection after major hepatic resection. On the other hand, the extent of the hepatectomy may shift the balance between PN and EN. At this stage, the different nutritional solutions and study designs do not allow a conclusive statement.

This first systematic review of prospective, randomized trials on EN and PN following liver resection reveals several drawbacks that preclude further conclusions. The studies suffer from insufficient patient volume as well as heterogeneity of the patient populations and nutritional protocols. Moreover, data analysis and definition of target variables do not allow a more detailed analysis.

However, these studies are important, since they (1) present the little available data from prospective, randomized, controlled trials comparing EN and PN; (2) emphasize the feasibility of early EN and the potential of preserving the immunological competence of the gastrointestinal tract, and (3) stress the potential importance of preoperatively defining subgroups regarding liver function and extent of hepatectomy.

More randomized trials are needed in order to substantiate or abrogate the so far unproven hypothesis of an improved outcome with EN following liver resection.

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