Neonates with gastrointestinal insufficiency or anatomical short bowel syndrome are dependent on TPN for survival. 6-8 TPN in these patients can result in the development of progressive liver disease from parenteral nutrition associated liver disease (PNALD), which can result in mortality.7,8 Soybean oil-derived n-6 fatty acids are implicated in the pathogenesis of PNALD, and it has been suggested that substitution of n-6 fatty acids with n-3 fatty acids will reduce the
occurrence of PNALD as a result of the beneficial effects on bile flow, immune function, and steatosis.

This report will review the evidence for the clinical and cost-effectiveness of n-3 lipids for pediatric and adult patients receiving parenteral nutrition.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of n-3 lipids for pediatric and adult patients on total parenteral nutrition?

2. What is the cost-effectiveness of n-3 lipids for pediatric and adult patients on total parenteral nutrition?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2004 and January 2009, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs), observational studies, and economic evaluations.

SUMMARY OF FINDINGS:

The literature search identified revealed 10 RCTs, four observational studies, and one economic evaluation. No health technology assessments or systematic reviews were identified.

Health technology assessments
No health technology assessments were identified.

Systematic reviews and meta-analyses
No systematic reviews or meta-analyses were identified.

Randomized controlled trials

Berger et al. (2008) examined the clinical impact of fish oil in patients requiring parenteral nutrition after abdominal aorta aneurysm surgery in a double-blind RCT. Twenty-four patients were randomized (method not described) to receive parenteral nutrition containing Lipofundin (50% MCT, 50% LCT; n=12) or Lipoplus (50% MCT, 40% LCT, 10% fish oil; n=12) at a dose of 0.15 g fat/kg/day. Patients in the fish oil group had a trend toward lower temperature (p=0.09), reduced hospital stay (9.9 versus 11.3 days, p=0.19), and reduced ICU stay (24 versus 35 hours, p=0.22). No differences were noted in liver function tests or glucose metabolism.
Friescke et al. (2008) hypothesized that parenteral nutrition with a higher n-3/n-6 ratio would attenuate systemic inflammation, providing beneficial impact on clinical outcomes. This single-centre double-blind RCT enrolled 166 adults admitted to the intensive care unit (ICU) with indication for parenteral nutrition. Patients were randomized to receive parenteral nutrition containing either Lipofundin MCT (a 1:1 mixture of MCT and LCT; n-3/n-6 ratio of 1:7; n=83) or 83% Lipofundin MCT and 17% Omegaven (fish oil; n-3/n-6 ratio of 1:2; n=83) for 7 days. Randomization was performed by computer-generated block randomization, and groups were stratified based on the presence or absence of systemic inflammatory response syndrome (SIRS). Sample size calculation was based on interleukin-6 (IL-6) differences noted in a previous study. Results were analyzed using both intention to treat and per protocol analysis. Using either analysis, no differences were found in IL-6 (measured as a marker of inflammation), monocyte human leukocyte antigen DR (HLA-DR; measured as a marker of immunosuppression), nosocomial infections, duration of mechanical ventilation, length of ICU stay, mortality, bleeding events, or organ function between treatment groups, indicating that the increased n-3/n-6 ratio did not affect inflammation or clinical outcome. The authors commented that the heterogeneous population may have contributed to the lack of effect noted.

Liang et al. (2008) conducted a double-blind RCT to assess whether parenteral supplementation of n-3 fatty acids postoperatively improved inflammatory and immunological function of colorectal patients and their clinical outcomes. Forty-one patients with colon or rectal cancer undergoing radical resection were randomized (computer-derived block randomization) to receive TPN containing either soybean oil alone (n=21) or a combination of soybean oil and fish oil (n=20) for seven days after surgery. The control group received TPN containing 0.6 g soybean oil lipid/kg/day on day 1 after surgery, and 1.2 g soybean oil lipid/kg/day on days 2-7 after surgery. The intervention group received 0.5 g soybean oil lipid/kg/day and 0.1 g fish oil lipid/kg/day on day 1 and 1 g soybean oil lipid/kg/day and 0.2 g fish oil lipid/kg/day on days 2-7, resulting in an n-3/n-6 ratio of 1:3. No sample size calculation was reported. No statistically significant differences in mortality or infectious complications were noted. Patients receiving TPN with fish oil had shorter hospital stay (17.45 versus 19.62 days), but the difference was not statistically significant (p=0.19). A greater reduction in IL-6 levels was noted in the group receiving fish oil (p=0.039), and the ratio of CD4+/CD8+ was increased in the fish oil group (p=0.035). The authors concluded that postoperative supplementation may have a favorable effect on outcomes in colorectal cancer patients by lowering the magnitude of inflammatory responses and modulating the immune response.

Wang et al. (2008) conducted a double-blind RCT to compare the effects of n-3 and n-6 fatty acid emulsions in parenteral nutrition on the hyperinflammatory response and systemic disease sequelae in adult patients with severe acute pancreatitis. Forty patients with severe acute pancreatitis were enrolled within 72 hours of onset, and were randomized through computer-derived block randomization to receive parenteral nutrition containing either soybean oil (Lipovenos; n=20) or a combination of soybean oil and fish oil (Omegaven; n=20) with a n-3/n-6 ratio of 1:4. A sample size calculation was not reported. The duration of parenteral nutrition was 5 days. Patients received 0.8 g fat/kg/day on day 1 and 1 g fat/kg/day on days 2-5. A greater reduction on C-reactive protein (CRP; a protein involved in inflammation) was noted after 5 days in the group receiving fish oil (p<0.05). No statistically significant differences were noted in white blood cell (WBC) count or IL-6 concentrations. There was a non-significant trend toward greater reduction in SIRS and acute respiratory distress syndrome (ARDS) in the group receiving fish oil, as well as a statistically significant greater improvement in oxygen index (p<0.05). Patients receiving fish oil had fewer days in continuous renal replacement therapy (18 versus 26 days, p<0.05), and there was a trend toward shorter ICU and hospital stay. There were no significant differences in infectious complications. The authors concluded that attenuation of the
hyperinflammatory response can be obtained with n-3 fatty acid supplementation, leading to improved respiratory and renal function.

A prospective, randomized, double-blind, multicenter trial by Wichmann et al. (2007) evaluated the safety and effectiveness of Lipoplus, a lipid emulsion containing 50% MCT, 40% LCT, and 10% fish oil (n-3/n-6 ratio of 1:2.7). Two hundred and fifty-six adults undergoing elective abdominal surgery were randomized to receive TPN supplemented with either Lipoplus (n=127) or Intralipid, consisting of 100% LCT (n=129) for 5 days. Patients received 0.7 g fat/kg/day on days 1 and 2 after surgery, and 1.4 g fat/kg/day on days 3-5 after surgery. The method of randomization was not described, and a sample size calculation was not reported. No differences in postoperative morbidity, mortality, or length of stay in ICU were noted between treatment groups. However, the group receiving TPN containing fish oil had reduced length of hospital stay (17.2 versus 21.9 days, p=0.0061). Patients receiving TPN containing fish oil also had higher levels of leukotriene B\textsubscript{5} (LTB\textsubscript{5}) and isomers (p=0.0035) and increased LTB\textsubscript{5}/LTB\textsubscript{4} ratio (p=0.0017). The authors commented that the observed increase in LTB\textsubscript{5} supports the notion of a smaller degree of pro-inflammation in the group receiving TPN supplemented with fish oil.

Grimm et al. (2006) investigated the anti-inflammatory and immunomodulatory effects of SMOFlipid (soybean oil, MCT, olive oil, and fish oil) in a double-blind RCT conducted in two centers. Thirty-three patients undergoing major abdominal surgery received post-operative TPN containing SMOFlipid (60 g/L soybean oil, 60g/L MCT, 50 g/L olive oil, 30g/L fish oil; n-3/n-6 ratio 1:2.3; n=19) or Lipovenoes (soybean oil 200 g/L; n-3/n-6 ratio 1:6.4; n=14). The total dose of lipid was 1.5 g/kg/day. The method of randomization was not described, and a sample size calculation was not reported. SMOFlipid enhanced release of LTB\textsubscript{5} and lowered LTB\textsubscript{4}, leading to a higher LTB\textsubscript{5}/LTB\textsubscript{4} ratio which the authors said suggests immunomodulatory and anti-inflammatory effects. The fish oil-containing lipid emulsion also reduced the length of hospital stay (13.4 versus 20.4 days, p<0.05).

In a multicenter double-blind RCT, Mertes et al. (2006) examined the safety and efficacy of SMOFlipid compared to a soybean oil emulsion. Two hundred and forty-nine patients undergoing elective abdominal or thoracic surgery with an indication for postoperative TPN were randomized in blocks of four by generation of random numbers to receive TPN providing 1.5 g fat/kg/day of either SMOFlipid (n=126) or Lipovenoes (soybean oil; n=123). A sample size calculation was performed, and both intention to treat and per protocol analyses were performed. There was a non-significant trend toward lower levels of the liver enzymes aspartate and alanine aminotransferases (AST and ALT) and alkaline phosphatase (AP) in the group receiving SMOFlipid (p-value not stated), indicating less alteration in hepatic function. There was also a non-significant trend toward shorter length of stay (15.7 versus 17.8 days; p-value not stated) in the SMOFlipid group. No effect on mortality was noted.

Klek et al. (2005) conducted a single-centre RCT to analyze the clinical impact of parenteral nutrition including glutamine or n-3 fatty acids. No indication was given as to whether this study was blinded, and the method of randomization was not described. One hundred and five patients undergoing surgery for gastric carcinoma were enrolled in the study, and 90 of these patients were included in the analysis. Patients were randomized to receive standard parenteral nutrition including a mixture of MCT and LCT (n=35), standard parenteral nutrition plus glutamine (n=34), or standard parenteral nutrition plus fish oil (Omegaven, 1 ml/kg/day; n=36) for at least 7 days after surgery. It was found that parenteral nutrition supplemented with fish oil led to faster increases in pre-albumin levels (p=0.02) and a trend toward increased total lymphocyte count (TLC; p >0.05), which suggested improved protein synthetic capability and
immunostimulation. There was also a non-significant trend toward fewer postoperative complications (26.6% versus 36.6%, p=0.2) and shorter hospital stay (14.4 versus 16.4 days) in the fish oil group compared to the group receiving standard parenteral nutrition.

A double-blind RCT by Heller *et al.* (2004) enrolled 44 patients receiving TPN for 5 days after undergoing surgery for carcinoma of the gastrointestinal tract or pancreas. Patients were randomized through computer-generated block randomization to receive TPN containing Lipovenoes (soybean oil; 0.8 g/kg/day on day 1, 1.0 g/kg/day days 2-5; n=20) or Lipovenoes (0.64 g/kg/day on day 1, 0.8 g/kg/day days 2-5) plus Omegaven (fish oil; 0.16 g/kg/day on day 1, 0.2 g/kg/day days 2-5; n=24). The sample size was calculated to detect a 25% reduction in AST. The group receiving fish oil had significant decreases in AST, ALT, bilirubin, and lactate dehydrogenase over the observation period, indicating liver protective effects. There were no differences in ICU stay, hospital stay, simplified acute physiology score (SAPS) II, gastrointestinal function, acute-phase inflammation markers, WBC count, body temperature, need for antibiotics, or complication rates between treatment groups. No differences were found in quality of life, health status, or mortality when patients were followed up after 18 months.

In a double-blind RCT by Antébi *et al.* (2004), 20 patients undergoing major surgery were randomized to receive TPN containing SMOFlipid enriched with α-tocopherol (200 mg/L; n=10) or Lipoven (soybean oil; n=10) at a dose of 1.5 g fat/kg/day for 5 days after surgery. Liver enzymes increased in both groups, but more in the control group. There were significant increases in ALT, γ-glutamyl transferase (γ-GT), AP, and CRP in the control group, indicating hepatic damage and inflammation, whereas the increases in ALT and CRP in the SMOFlipid group were not statistically significant. The authors concluded that the results suggested that ongoing alterations in liver function by TPN are lessened in patients receiving SMOFlipid.

**Observational studies**

Heller *et al.* (2006) conducted an open-label, prospective, multi-center study to evaluate dose-dependent effects of parenteral nutrition supplemented with fish oil on disease and end-organ related outcomes. Six hundred and sixty-one patients in 82 German hospitals who had received TPN including fish oil for at least 3 days regardless of underlying diagnosis were included in the study. The dosage of fish oil was at the discretion of the attending physician. After adjustment for age, SAPS II, mortality, and daily caloric intake, it was found that a dose of fish oil of >0.05 g/kg/day was associated with reduced length of ICU and hospital stay. Fish oil doses between 0.15 and 0.2 g/kg/day were associated with reduced antibiotic use compared to doses <0.15 g/kg/day and improved survival was noted in patients receiving 0.1-0.2 g/kg/day fish oil compared to patients receiving <0.05 g/kg/day after adjustment for age, SAPS II, and daily caloric intake. In this study observing patients supplemented with fish oil, mortality rates were lower than predicted based on SAPS II (observed rate of 11.9% versus expected rate of 18.9%, p<0.001). The lack of placebo group and defined dose limit the conclusions that can be drawn from this study. Additional post-hoc analysis suggested that fish oil administered as part of parenteral nutrition had most favorable effects when the n-3/n-6 ratio was less than 1:2.

Two case reports including a total of three infants receiving TPN supplemented with fish oil have been reported. In each of these cases, the infants were dependent on TPN but developed cholestasis PNALD. As such, n-6-containing lipids were replaced with n-3-containing fish oil. In each case cholestasis and PNALS were reversed, and CRP levels returned to normal. One infant who had been on the list for liver transplant was removed from the list. In one case report the infant initially received 0.2 g/kg/day fish oil, and the dose was gradually increased to 1.5 g/kg/day. The other two infants reached a maximum fish oil dose of 1 g/kg/day.
Tsekos et al. (2004) conducted a retrospective analysis of 249 patients to assess perioperative and postoperative TPN including fish oil in critically ill patients. Patients who underwent major abdominal surgery and required postoperative TPN were included. Group 1 received parenteral nutrition containing a mixture of MCT and LCT (1:1 mixture; 0.6g/kg/day). Groups two and three had part of the lipid emulsion replaced with Omegaven (fish oil); group two received only postoperative TPN, whereas group three received both preoperative and postoperative TPN. Patients receiving fish oil before and after surgery had reduced mortality compared to patients receiving standard TPN (p<0.02). There were also fewer deaths in patients receiving fish oil only after surgery compared to patients receiving standard TPN, but the difference was not statistically significant. Patients receiving fish oil before and after surgery had a lower incidence of mechanical ventilation (17 versus 31%, p<0.05) and reduced length of hospital stay (22.2 versus 29.2 days, p<0.05) compared to patients receiving standard TPN. Patients receiving fish oil either postoperatively or both preoperatively and postoperatively had reduced readmission to ICU compared to patients receiving standard parenteral nutrition (5% versus 17%, p<0.05). The retrospective observational study design limits conclusions that can be drawn from this study.

Economic evaluations

The RCT by Klek et al. (2005) also included a cost-effectiveness analysis. The study was conducted in Cracow, Poland, and the currency is the Polish Zlotych (PLN), also reported in Euros. The cost-effectiveness analysis appeared to be carried out from the perspective of the healthcare provider. No details were given on the breakdown of the cost, and no statistical analysis was reported. Since there was no summary of health benefits, the study included a cost-consequence analysis rather than cost-benefit analysis. The costs of parenteral nutrition, hospital stay alone, and total cost in the group receiving n-3 fatty acids were 32,780 PLN (6689 Euro), 16,800 PLN (3360 Euro), and 49,580 PLN (10 550 Euro), respectively. The costs of hospital stay alone and total cost in the group receiving standard parenteral nutrition were 18,600 PLN (3770 Euro), and 39,480 PLN (8400 Euro), respectively. The authors commented that parenteral nutrition including Omegaven was almost twice as expensive as standard parenteral nutrition, and it was doubtful whether the treatment was cost-effective. They concluded that the cost of immunostimulation treatment based on n-3 fatty acids is higher than the cost of standard parenteral nutrition, and the difference exceeds potential profits from shorter hospital stay.

Limitations

No RCTs were identified that examined the clinical effectiveness of n-3 fatty acids in pediatric patients with PNALD. These studies would be needed before n-3 fatty acids can be recommended in pediatric patients receiving TPN. Furthermore, each RCT identified which examined the clinical effectiveness of n-3 fatty acids in adult patients excluded patients with liver failure, limiting the generalizability of these studies to pediatric patients with PNALD.

Although a number of RCTs were identified examining the clinical effectiveness of n-3 fatty acids in parenteral nutrition in adult populations, many of these had small sample sizes leading to low power to detect significant differences compared to controls. Meta-analysis of these studies would be useful, but differences between these studies likely limit the feasibility of combining the data in a statistical fashion. For example, the described RCTs used differing formulations of fish oil-containing lipid emulsions. Some contained only fish oil and soybean oil, whereas others also incorporated MCT and/or olive oil. Furthermore, there was variation in dosage, duration of treatment, and patient populations. It is also unclear as to
whether benefits observed with lipid emulsions containing soybean oil, MCT, olive oil, and fish oil were due to fish oil or the other components.\textsuperscript{14,15,16}

Only one economic evaluation was identified.\textsuperscript{16} However, this evaluation was based on a study that found little clinical benefit to inclusion of n-3 fatty acids in parenteral nutrition. Cost-benefit analysis is needed to confirm whether the incorporation of fish oil in parenteral nutrition regimens is cost-effective. Furthermore, since the economic evaluation was not a Canadian study, it may not be generalizable to the Canadian healthcare setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

This report identified 10 RCTs, four observational studies, and one economic evaluation evaluating the clinical and cost-effectiveness of n-3 fatty acids in parenteral nutrition. All studies found fish oil to be safe and well-tolerated, with no negative impact on clinical outcomes.

Observational studies suggested that inclusion of n-3 fatty acids in parenteral nutrition reduced mortality in adult patients,\textsuperscript{19,22} but this was not confirmed in RCTs\textsuperscript{10,11,13} possibly due to inadequate sample size. Several studies showed actual, or a trend toward, reduced hospital or ICU stay in patients receiving parenteral n-3 fatty acids.\textsuperscript{9,11,13-16,19,22} Evidence for the anti-inflammatory effects of parenteral n-3 fatty acids was provided through reports of reduced IL-6 and CRP levels and increased 5-series leukotrienes, although some studies found no effect.\textsuperscript{10-14,17} The reason for the discrepant findings related to inflammation is not clear. All studies examining LTB\textsubscript{5} suggested anti-inflammatory effects of parenteral n-3 fatty acids\textsuperscript{13,14}, whereas only one of three studies reporting IL-6 values reported a reduction.\textsuperscript{10,11,23} Therefore, conclusions regarding the anti-inflammatory effects of n-3 fatty acids may be related to the measurement used. Additionally, one study reporting no effect on inflammatory markers had a heterogeneous population, possibly contributing to the lack of effect.\textsuperscript{10}

Although the identified studies generally point to beneficial effects associated with the inclusion of n-3 fatty acids in parenteral nutrition in adult populations, larger RCTs and/or systematic reviews/meta-analyses are needed to clarify these effects. At this point economic evaluations do not support the cost-effectiveness of parenteral n-3 fatty acids, but cost-benefit analyses are needed.

The only studies that were identified assessing the effectiveness of n-3 fatty acids in pediatric populations were case reports.\textsuperscript{6,21} Although these reports indicated reversal of PNALD and removal from the liver transplant list, RCTs are needed to confirm these findings.

In conclusion, the literature included in this report support the safety of inclusion of n-3 fatty acids in parenteral nutrition, and some, but not all, studies report improved clinical outcomes. The choice to include n-3 fatty acids in parenteral nutrition regimens must take into consideration whether the increased cost is outweighed by potential clinical benefit in a given patient population.

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