Perioperative Use of Arginine-Supplemented Diets: A Systematic Review of the Evidence
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Journal of the American College of Surgeons 2011; 212(3):385-399

Objective
To conduct a systematic review of all randomized clinical trials evaluating arginine-supplemented diets in elective surgical patients.

Methods
Meta-analysis included randomized clinical trials of elective surgical patients comparing enteral nutrition supplemented with arginine (with or without other immune-modulating agents) versus standard enteral nutrition, and reported clinical outcomes. The primary outcome of interest was number of patients with new infectious complications, and secondary outcomes included hospital length of stay (LOS) and mortality. Elective surgical patients were defined as those undergoing a scheduled surgical procedure whether or not they were cared for in a critical care environment. Studies of critically ill patients undergoing emergent operations were excluded.

Subgroup analysis included (1) GI vs. non-GI surgery (2) upper GI surgery vs. lower GI surgery vs. mixed (both upper and lower) GI surgery (3) IMPACT® formulas vs. other arginine-supplemented (non-IMPACT®) formulations and (4) pre- vs. post- vs. perioperative use of arginine-supplemented diets.

Study Characteristics
- 35 elective surgical patient studies were included in the review.
- 25 studies included elective GI surgery and 10 studies included other elective surgical procedures.
  - Of the 25 GI surgery studies, 18 studies reported upper GI surgery only, 2 reported lower GI surgery only, and 5 studies reported mixed (upper and lower) GI surgery.
- 23 studies used IMPACT® formulas and 12 studies used other (non-IMPACT®) formulations
- Use of arginine-supplemented diets was exclusively reported preoperatively in 7 studies, postoperatively in 18 studies, and perioperatively in 13 studies.

Results
- Arginine-supplemented diets were associated with considerably reduced overall infectious complications when compared with standard formulas across elective surgeries, based on 28 studies reporting infectious complications on a per-patient basis (RR=0.59; 95% CI, 0.50-0.70; P<0.00001). This equates to a 41% observance in the reduction of infectious complications. The test for heterogeneity was not significant. (P=0.11, I²=26%).
  - Arginine-supplemented diets were associated with a significant reduction in infectious complications compared to standard diet therapies in the 16 upper GI only studies (RR=0.69; 95% CI, 0.55-0.87; P=0.002), the 1 study of lower GI surgery (RR=0.34; 95% CI, 0.17-0.68; P=0.002), and 4 studies of mixed GI surgery (RR=0.49; 95% CI, 0.36-0.66; P<0.0001). Differences between these subgroups were not statistically significant (P=0.06).
  - The use of IMPACT® formula was associated with significantly fewer infectious complications in the 21 trials that reported on outcomes (RR=0.49; 95% CI, 0.41-0.58; P<0.00001) compared to the use of non-IMPACT® formulations reported in 7 other trials (RR=0.95; 95% CI, 0.75-1.21; P=0.68). The differences between these 2 subgroups was statistically significant (P<0.0001).
  - Patients fed the arginine-supplemented diets pre-, post- and perioperatively experienced fewer infectious complications compared to standard diet therapies (P=0.03). However a greater treatment effect was seen with the perioperative administration of arginine-supplemented diets (RR=0.46; 95% CI, 0.36-0.59; P<0.00001) compared to preoperative (RR=0.57; 95% CI, 0.37-0.88; P=0.01), and postoperative (RR=0.78; 95% CI, 0.64-0.95; P=0.01). The difference between the subgroups was significant (P=0.03).
Results (continued)

• Overall hospital LOS, aggregated across 29 studies, was reduced in both elective GI and non-GI surgical patients receiving arginine-supplemented diets when compared with patients receiving standard formulas (WMD=-2.38 days; 95% CI, -3.39 to -1.36; \( P<0.00001 \)). The test for heterogeneity was significant (\( P<0.00001, \, I^2=87\% \)).

  o Arginine-supplemented diets were associated with a significant reduction in hospital LOS in the 14 upper GI studies (WMD=-2.12 days; 95% CI, -3.85 to -0.39; \( P=0.02 \)), and in the 5 studies of upper and lower GI studies (WMD=-2.36 days; 95% CI, -3.09 to -1.64; \( P<0.00001 \)). The 2 studies of lower GI only surgery did not show the same effect (WMD=-.74 days; 95% CI, -3.92 to -2.45; \( P=0.65 \)). There were significant differences between these subgroups (\( P=0.004 \)).

  o The use of IMPACT® formula was associated with a significant reduction in hospital LOS in the 21 trials that reported on outcomes (WMD=-2.62 days; 95% CI, -3.65 to -1.59; \( P<0.00001 \)) compared to the use of non-IMPACT® arginine-supplemented formulations reported in 8 other trials (WMD=-0.89 days; 95% CI, -3.21 to -1.44; \( P=0.45 \)). The difference between these 2 subgroups was statistically significant (\( P<0.00001 \)).

  o Arginine-supplemented diets were associated with a significant reduction in hospital LOS in the 11 studies of perioperative intervention (WMD=-2.38 days; 95% CI, -3.44 to -1.32; \( P<0.0001 \)), and in the studies of postoperative intervention (WMD=-2.34 days; 95% CI, -3.80 to -0.65; \( P=0.006 \)) but there was no significant effect in 6 studies of preoperative alone interventions (WMD=-1.38 days; 95% CI, -3.49 to -0.73; \( P=0.20 \)). There were significant differences between subgroups, suggesting a greater benefit to the perioperative administration of arginine-supplemented diets (\( P=0.001 \)).

• Arginine-supplemented diets did not have a significant effect on mortality (RR=1.08; 95% CI, 0.65-1.80; \( P=0.76 \)) based on the 21 studies that reported mortality as one of the outcomes.

Conclusion

• The use of nutrition therapy containing arginine and omega-3 fatty acids used perioperatively in elective surgical patients is associated with a substantial reduction in infection and shorter LOS.

• A hypothesis generating sub-analysis found increased benefit of IMPACT® vs. non-IMPACT® arginine-supplemented formulas based on outcomes of infectious complications and/or LOS.