Pharmacological treatment of postoperative appetite loss

This supplemental digital content describes in detail the available evidence of pharmacological treatment options for postoperative appetite loss.

Alvimopan

Alvimopan is a peripherally acting µ-opioid antagonist that is administered orally beginning the day before surgery and twice a day afterwards. It has a very limited oral absorption capacity and does not readily cross the blood-brain barrier. In 2001, an early randomized, placebo-controlled trial showed that Alvimopan reduces the time necessary to return to gastrointestinal function without compromising the analgesic effects of opioids when introduced under the name ADL 8-2698 into surgical practice. Subsequent multicenter, randomized, double blind, placebo-controlled trials in the United States found positive evidence for a shortened time to return of bowel function; however, these results could not be replicated in Europe. A meta-analysis of nine randomized controlled trials involving 4,075 patients showed that Alvimopan can accelerate recovery of gastrointestinal function without compromising opioid analgesia with a preferred dose of 12mg (compared to 6mg). However, appetite was not an endpoint in these studies, which were limited to patients with bowel resection, hysterectomy, or cystectomy. Thus the effect of Alvimopan on appetite remains questionable, despite its positive influence on (lower) gastrointestinal function.

5-HT4-receptor-agonists

Mosapride citrate, an agonist of 5-Hydroxytryptamine receptor type 4 (5-HT4, ), has been applied at a dose of 15mg/day to patients five years after vagal nerve preserving distal gastrectomy reconstructed by interposition of a jejunal j pouch with a jejunal conduit for early gastric cancer. After three months of mosapride citrate therapy, the proportion of patients...
reporting no change in appetite compared to before the operation increased from 78.3% (n=15 of 18) to 100%, but this change did not reach statistical significance. Similar results, but with a statistically significant increase in appetite after therapy, were found earlier by the same group using 7.5 to 15mg of cisapride daily for three months in patients with a mean of 1.3 years after Billroth I distal gastrectomy for early gastric cancer. However, cisapride has been removed from the market in most countries, due to a correlation with severe cardiac side effects.

Octreotid

Somatostatin analog Octreotide at a dose of 100µg subcutaneously increased postprandial appetite measured by VAS of hunger and serum-GLP1 in patients at a mean of 2.5 years after esophagectomy. However, it failed to change appetite after fasting, or in healthy controls.

Cannabinoids

Cannabinoids are known to improve appetite. Bakshi and Barett recently reviewed the use of cannabinoids in surgical patients. They described cannabinoid medications such as Dronabinol and Nabilone but did not find quantitative evidence for the use of cannabinoids to improve appetite in surgical patients. Apart from surgical application, Dronabinol has been found to be an effective appetite stimulant in patients with AIDS. It is usually administered orally, as an oil. In practice, 2.5mg (=0.1ml) may be put on a sugar cube or in coffee cream, with a daily dose of 10mg usually being sufficient. Appetite stimulation takes place after 30–60 minutes and lasts for approximately 24 hours. The synthetic cannabinoid Nabilone has been used to treat loss of appetite or nausea in non-surgical patients, but data on efficacy and safety are inconsistent, so larger randomized controlled trials are necessary.
Steroids

A randomized, controlled, double-blind trial found that low-dose anabolic steroids (such as nandrolone decanoate) provided no therapeutic benefit, including increased appetite, for patients who underwent esophagectomy for cancer 15.

Outside of surgical applications, the corticosteroid dexamethasone has long been used as a potent appetite enhancer in cancer-related cachexia. However, corticosteroid-type toxicity may lead to drug discontinuation or patient refusal 16. Furthermore, we found no studies on the postoperative effects of corticosteroids.

Ghrelin

As described in detail earlier, the peptide hormone ghrelin plays a central role in appetite regulation. Synthetic ghrelin use has been shown to increase appetite in patients with cachexia from cancer, chronic obstructive pulmonary disease, congestive heart failure, and end-stage renal disease with dialysis, among other conditions 17. Serious adverse events were described as extremely rare, with mild adverse events occurring in about 20% of patients, with flushing (10%) being the most common. However, flushing seldom led to discontinuation of ghrelin administration 18. As a severe drawback, ghrelin cannot be administered per os, but oral ghrelin-agonist development is underway and initial studies have demonstrated its positive effects on cancer-related cachexia 19.

A number of surgical research trials, including several published by a group in Osaka, have examined the use of ghrelin in treating appetite loss after major abdominal surgery. In a randomized, placebo-controlled phase II study, the Osaka group administered synthetic ghrelin intravenously twice a day for 10 days after resuming oral food intake in the immediate postoperative course following total gastrectomy for cancer. Ghrelin improved appetite and food intake and lessened postoperative weight loss 20. The same group then performed a study with the same design on patients who underwent esophagectomy with gastric tube reconstruction and found a non-significant tendency towards increased appetite and significantly less postoperative weight loss 21. An additional cohort study on patients suffering
from severe weight loss (>15%) more than one year post gastrectomy showed that appetite as well as weight improved after ghrelin administration.  
Another group compared lean and obese subjects with patients at least 12 months after gastrectomy for cancer. Ghrelin lead to increased appetite in lean subjects and normalized appetite in obese subjects, but did not change appetite or energy intake in gastrectomy patients. These results are in line with another study that could not reproduce a positive effect of ghrelin on appetite after gastric or esophageal surgery with vagotomy.

In summary, there is evidence that ghrelin administration leads to an improved appetite in the immediate postoperative period, but not in the long-term. However, despite the availability of randomized controlled trials, quantitative data synthesis was not possible because of the heterogeneity of measurement endpoints, ghrelin treatment protocols, and time since operation. Furthermore, due to the current absence of oral applications of ghrelin, it cannot be considered a long-term treatment. Finally, because ghrelin has only been studied in phase II trials thus far, it is not available for routine use.

Rikkunshito

Rikkunshito is a traditional Japanese herbal medicine that is also known under its Chinese medicine name Liu-jun-zi-Tang. It has been reported to improve postoperative appetite after gastrointestinal surgery by increasing plasma ghrelin levels and as having positive effects on cancer-related symptoms. Three prospective studies have assessed the postsurgical effects of Rikkunshito as a component of alternative medicine. Takiguchi et al. showed that Rikkunshito significantly improved appetite in gastric cancer patients at least 6 months and up to 5 years after surgery. The patients received 2.5 g of Rikkunshito before every meal, i.e., three times daily, for 4 weeks. VAS ratings after four weeks showed an improvement in appetite, but EORTC QLQ-C30 scores showed no effect. Gunji et al. assessed long-term quality of life in patients at least 6 months after proximal gastrectomy with the same protocol but found no significant improvement of appetite. Nakamura et al. investigated the effects of Rikkunshito in patients 4 weeks after esophagectomy with gastric
reconstruction in a non-randomized design. A 48-week treatment regimen consisting of 2.5 g of Rikkunshito administered before every meal showed no significant improvement of appetite loss, although there was significantly less body weight loss in the Rikkunshito group than in the control group, as well as a trend towards less appetite loss four and 13 weeks after beginning treatment with Rikkunshito 28. Overall, the impact of Rikkunshito on appetite loss is not sufficiently documented. More prospective studies, especially randomized, placebo-controlled trials are necessary.

Other

A study on gallbladder motility showed that oral application of erythromycin had no effect on appetite after a test meal for patients with a median of 2.5 years after gastrectomy, whereas erythromycin led to a nonsignificant trend of improved appetite in healthy controls 29.

A retrospective study on patients with colorectal cancer, most of whom had undergone surgery, showed that complementary treatment with oral enzymes alone, but not in combination with another complementary treatment, reduced disease signs and symptoms including appetite changes 30.
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