Perioperative Synbiotic Treatment to Prevent Postoperative Infectious Complications in Biliary Cancer Surgery: A Randomized Control Trial

To the Editor:

We read with interest the study by Sugawara et al,[1] which concluded that preoperative oral administration of synbiotics is likely to reduce postoperative infectious complications after hepatobiliary resection of biliary tract cancer.

The trial design is adequate for drawing conclusions regarding the timing of synbiotic dosing for patients undergoing surgery; however, the absence of a placebo significantly limits its ability to describe the efficacy of nutritional supplements in the reduction of postoperative complication rates. This is compounded by the fact that the study is not blinded. Furthermore, the method of randomization is not explained, and no evidence is presented to suggest sample sizes were considered. This makes many of the conclusions drawn by the authors difficult to justify.

Patients in past trials of functional foods have complained of side effects, such as diarrhea or altered bowel habit,[2] but sadly no mention is made of synbiotic tolerance or withdrawals from the study due to side effect profiles. This is important if we are expecting our patients to take a 2-week course of this treatment preoperatively. A more major concern has been the potential for sepsis caused by the treatment organisms,[3,4] especially in immunocompromised patients and those undergoing surgery. In this study, blood cultures were taken if patients had a temperature greater that 38.5°C, yet the authors do not report the species that were grown in the 6 patients that were found to be bacteremic. If synbiotics are to be accepted by the surgical community, it is important that these data are reported in all future trials.

The number of viable bacteria reaching or colonizing the intestine depends on many factors other than dose, particularly the probiotic formulation, coadministration of food, gastric pH, intestinal motility, and prior composition of intestinal microbiota.[5] Patients were fed enterally via jejunal feeding tubes, and the authors state that parenteral nutrition was also supplied by a central venous catheter. But it is unclear which parenteral feed was used and what proportion of patients were fed in this manner. This has the potential to dramatically alter the efficacy of any synbiotic, and these data should be presented in future trials.

It is interesting to note that the study did not demonstrate a statistically significant increase in the fecal population of the *Lactobacillus* strain. The importance of this has been contested because *Lactobacilli* may persist within colonic mucosa even after its disappearance from fecal samples.[6] However, it has also been shown that *Lactobacilli* probiotics are largely digested in the stomach, thus reducing their efficacy.[7,8] This study adds weight to this belief, as it only demonstrated a significant increase in the *Bifidobacterium* population, suggesting that the efficacious component of the synbiotic is provided by the galacto-oligosaccharide.

The authors claim that jaundice-related physical damage to the intestinal mucosa may be reversed with bile replacement rather than preoperative use of symbiotics; 75% of group A and 80.4% of group B underwent percutaneous transhepatic biliary drainage preoperatively and had this replaced orally or via a nasoduodenal tube. However, no subgroup data analysis is offered for those that did not undergo this procedure, all patients had a synbiotic at some point in the study, and no control group is used. Therefore, it is not possible to state whether the reduction in intestinal permeability and improved mucosal integrity is caused by biliary replacement alone or whether a synbiotic is in fact responsible for the protection of the intestinal mucosa.

Functional foods are a potentially significant development in the reduction of sepsis and the inflammatory response in patients undergoing major surgery. The study by Sugawara et al[1] represents progress in this area. However, it is vital that future trials of synbiotics adhere to the high standards required of randomized control studies to allow clear elucidation of their role.

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Hepatic Resection-Related Hypophosphatemia Is of Renal Origin as Manifested by Isolated Hyperphosphaturia

To the Editor:

Seven years ago, we prospectively investigated early postsurgical modifications of the calcium-PTH axis.[1] Following the article by Salem and Tray,[2] we retrospectively reexamined patients who underwent hepatic resection in our study and

for whom we had data on serum phosphate, ionized calcium, HCO_3^-, pH, and intact PTH determined before, during the first and second hours of surgery, and serially thereafter on postoperative days 1, 2, 3, 5, and eventually 7. Fractional phosphate excretion could be quantified before surgery from 12-hour urinary estimation and from 24-hour urinary estimation on postoperative days 1, 2, 3, 5, and eventually 7. The results are expressed as mean ± SEM.

Nine patients (7 women and 2 men), with a mean age of 42.5 ± 3.1 years, underwent liver resection for hepatic metastases secondary to colon cancer (n = 4), focal nodular hyperplasia (n = 3), giant hemangioma (n = 1), or hydatid cyst (n = 1). Hepatectomy mean duration was 205 ± 15 minutes, and mean intraoperative bleeding was 750 ± 171 mL. Six of 9 patients needed pedicle clamping (mean duration, 35.3 ± 5.7 minutes). All patients were extubated at the end of surgery. Five of 9 patients were admitted to the intensive care unit for 24 hours. Oral diet was allowed on postoperative day 3 for the majority of patients. No major complications occurred postoperatively, but 3 patients presented with transient fever associated with atelectasis. A decrease in serum phosphate was observed as early as the first and second hours during liver resection, from 1.25 ± 0.07 mmol/L (normal, 0.70–1.30 mmol/L) to 0.99 ± 0.04 and 1.02 ± 0.04, respectively. Serum phosphate reached a nadir on postoperative day 2 (0.49 mmol/L ± 0.10, $P < 0.001$), which represented a decrease of 60.8%. Serum phosphate at its nadir was inversely correlated with the number of liver segments removed ($P < 0.01$), but not with pedicle clamping duration ($P > 0.5$). Fractional phosphate excretion increased significantly on postoperative days 1 and 2, from 12.4% ± 1.2% (normal, 10%–15%) to 26.8% ± 1.1% and 35.6% ± 5.6%, respectively ($P < 0.05$), which represents a 116% to 187% increment. Fractional excretion of phosphate peaked on postoperative day 2 where it was correlated with the number of segments removed ($P < 0.01$) and inversely correlated with serum phosphate ($r = -0.49$; $P < 0.001$), but not with the duration of pedicle clamping ($P = 0.06$). Rapid changes in serum Ca^{2+} were noted at the beginning of the surgical procedure with a significant fall ($P < 0.01$) from 1.22 ± 0.009 mmol/L (normal, 1.16–1.29 for pH: 7.4) to 1.03 ± 0.01 mmol/L and 0.98 ± 0.01 mmol/L on the first and second hours (nadir) of surgery, respectively, before returning to its baseline level 36 hours after surgery. Intact PTH rose significantly ($P < 0.01$) during hepatectomy, from 3.4 ± 0.4 pmol/L (normal, 1.4–6.8 pmol/L) to 13.5 ± 2 and 25.5 ± 4.2 (7-fold increase) on the first and second hours of surgery, respectively, and declined thereafter to 9.7 ± 1.9 pmol/L 24 hours after surgery and to 4.7 ± 0.7 pmol/L (normal) at 36 hours. Intact PTH was not correlated with serum phosphate ($r = -0.17$; $P > 0.2$) but was inversely correlated with Ca^{2+} ($r = -0.61$; $P < 0.0001$) and significantly associated with fractional phosphate excretion, albeit with a limited degree of correlation ($r = 0.34$; $P < 0.05$). During the first 2 postoperative days, fractional phosphate excretion and PTH varied inversely, and the fractional phosphate excretion peaked when intact PTH returned to its normal values. Only 1 patient needed substitution for frank hypophosphatemia (0.25 mmol/L).

Hypophosphatemia after major hepatectomy was initially reported by Keushkerian and Wade in 1984,[3] but very few data have been published thereafter. Several physiologic mechanisms were evoked; however, dramatic urinary phosphate wastage was demonstrated recently by Salem and Tray.[2] Chronologically, lowered phosphatemia correlated better with urinary phosphate leakage than with an hypothetic process, such as phosphate shifting into cells like hepatocytes. Liver regeneration lasts no less than 4 weeks[4] and therefore cannot be a credible reason for transient hypophosphatemia that usually persists for 2 to 3 days. Since the mid-1990s, hypophosphatemia has been observed early after liver resection in our department. Phosphate monitoring is routinely performed with phosphate substitution when the serum level drops to less than 0.5 mmol/L. Like Salem and Tray,[2] we have observed similar postoperative variations of serum phosphate and its fractional excretion, which were progressively resolved by postoperative days 5 and 7. Salem and Tray stated that "posthepatic hypophosphatemia and its concomitant renal phosphate leak may well reflect the action of an as yet unidentified circulating agent responsible for phosphate homeostasis."[2] Similar phosphate metabolism disorders with hypophosphatemia and deficit of phosphate renal handling were noted in other pathologic settings, mainly X-linked hypophosphatemic rickets, autosomal-dominant hypophosphatemic rickets, and oncogenic osteomalacia.[5] The study of these disorders has resulted in the discovery of a number of proteins, which were named phosphatonins, fibroblast growth factor-23 (FGF-23), secreted frizzled related protein-4 (sFRP-4), and matrix extracellular phosphoglycoprotein (MEPE).[5] However, by controlling renal handling of phosphate in proximal tubules, PTH plays a central role in phosphate homeostasis.[5] Salem and Tray did not find any significant variation of PTH and FGF-23 using a carboxyl-terminal FGF-23 assay in 2 and 4 patients, respectively. The prospective and systematic monitoring we performed in our study showed PTH level increased 7-fold and peaked in the second surgical hour before returning to its baseline level by 36 hours. Intact PTH variation appeared to be inversely correlated with serum Ca^{2+} as an acute response to its changes during surgery. The plasma concentrations of Ca^{2+} and inorganic phosphate are primarily under the control of PTH and vitamin D.[6] Variations in Ca^{2+} are controlled by a specific Ca^{2+}-sensing protein in the cell membrane of parathyroid cells, leading to the desired changes in PTH secretion.[7] Through its effects on bone and intestinal absorption, PTH tends to augment phosphate entry into the extracellular fluid. As well, PTH is inclined to reduce proximal tubular phosphate reabsorption, resulting in increased fractional excretion. However, the urinary effect usually predominates in patients with relatively normal renal function, as PTH tends to lower the phosphatemia.[5] Knowing the rapid effect of PTH on proximal tubular phosphate reabsorption,[5] hyperphosphaturia after liver resection appears to be mediated by factors other than PTH. PTH and fractional excretion of phosphate were chronologically uncorrelated; their respective variations were reversed during the first 48 postoperative hours.

Hypophosphatemia with hyperphosphaturia appears to be a constant postoperative disorder after hepatectomy. Rapid hypocalcemia during surgical procedures is associated with increased PTH as an acute response. However, PTH

is chronologically unrelated with later urinary phosphate leakage. Therefore, posthepatectomy hypophosphatemia, as a consequence of elevated fractional excretion of phosphate, appears to be mediated by phosphaturic factors other than PTH. The role of phosphatonins (FGF-23, MEPE, and sFRP-4) in this setting was not yet well studied, an aspect that we are currently investigating.

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Mental Training in Surgical Education: A Randomized Controlled Trial

To the Editor:

We read with interest the recent paper by Immenroth et al regarding mental training during laparoscopic cholecystectomy courses.[1] We applaud the authors, although we suggest that their results are interpreted with caution.

Mental practice is generally considered to be a specific area within the broader domain of mental preparation. Professional sportsmen use a variety of mental techniques, such as visual imagery, mental relaxation, audiovisual instruction, and psyching-up strategies to ensure a level of preparedness for major tests of performance.[2,3] These do not all constitute mental practice in the sense suggested by Immenroth et al,[1] although they are purported to have a positive impact upon performance. In this study, the 2 treatment groups were both allowed 30 minutes to prepare themselves on the day of data collection. The practical groups were thus not isolated to solely use physical methods, perhaps confounding the results.

Furthermore, it has been suggested that any gain in performance attributed to mental practice may be a result of the increased motivation of a subject when placed in the treatment group.[4] This has led some investigators to question the relevance of a no-practice group, ie, a group that receives no contact with trainers between initial assignment to treatment and data collection. It is postulated that these individuals are likely to underperform when compared with those who have received "special attention." To correct this potential effect in this study, the authors may have enabled the control group to take part in an unrelated activity within the same time period, for example, a motivational lecture on surgical careers. Within the study, differences between the groups may be attributable to the motivation of the treated participants.

With regard to the interpretation of the data, the mental rehearsal group improved to a significantly greater extent than the other 2 groups on a task-specific checklist. There was no concomitant improvement in terms of the global rating scale, a more reliable and valid measure of technical skill.[5] Previous studies have suggested checklists to be inferior measures of technical skill, with poor inter-rater reliability, being better suited as measures of whether an action has been committed rather than the quality of a defined action. Checklists are thus a reflection of one's knowledge, rather than ability to perform the defined task. This is a suitable measure for assessing improvements hypothesized by mental training, but not an ideal evaluation of the effect of practical training. It is surprising that the practical training group did not improve their global rating scores. Perhaps the training sessions were too short to show such improvements. Furthermore, were the additional practical training sessions administered by expert faculty, or were the subjects left to train alone? It has been shown that practical training without a tutor does not necessarily improve technical performance and, indeed, may be detrimental to outcome if the tutee repeatedly practices incorrect actions.[6]

Although cognitive training is a crucial, and perhaps neglected, aspect of surgical education research, this has to go hand-in-hand with practical exposure. The authors must be commended on reinstating the importance of cognitive training within the surgical literature, but we fear they are neglecting the interaction between these 2 modes of acquiring surgical skill. It would have been useful to comment on the reinforcement of detail learnt during mental rehearsal at subsequent training sessions. This may be possible with the simple addition of didactic material at the beginning and end of further practical sessions. A further benefit to be assessed is whether this type of training can reduce the effect of skills decay, or even improve the performance of experienced surgeons during more complex, and rarer, cases.

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