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Initiating a Practice Change: Prescribing Probiotics in Surgical Patients

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Abstract | **Review Article**

Background: The intestinal microflora is thought to be the origin for many infectious complications seen in surgical conditions, due to dysfunction of the intestinal barrier and bacterial translocation. Probiotics may produce beneficial effects on the intestinal barrier function and help reduce the incidence of infectious complications in this group of patients.

Keywords: Probiotics, surgery, complications, infection.

INTRODUCTION

The use of probiotics as potential therapy has been proposed for a variety of medical and surgical conditions. World Health Organization as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host", probiotics have many potential ways in which to exert influence on the body. Whilst much of the work involving probiotics has focussed on reducing the incidence of antibiotic-associated ted diarrhoea and Clostridium difficile (C. difficile) infection, the prevention of post-operative infectious complications in surgical patients is another novel application. With the use of prophylactic antibiotics to reduce rates of infections following surgery and the increasing problem of multi-resistant organisms, new strategies are being sought to improve outcomes. The "gut origin of sepsis hypothesis" and possible role of bacterial translocation in post-operative sepsis have raised the question as to whether or not probiotics could also be of benefit in such patients. Particular focus will be given to the use of probiotics in acute pancreatitis and the recent surrounding controversies.

Heterogeneity of Probiotics

Some studies have also looked at the use of synbiotics, which are combinations of prebiotics and probiotics aiming for a synergistic effect. Prebiotics are "selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confer benefits upon host well-being and health". Unlike probiotics, which contain live bacteria as their active ingredients, prebiotics are carbohydrates that are resistant to digestive enzymes and therefore reach the colon and act a fermentable "food source" for the resident bacteria. As summarised by Kolida *et al.*, prebiotics have been shown to increase numbers of beneficial Bifidobacteria and Lactobacilli, decrease numbers of potentially harmful bacteria including E. Coli and Clostridium, as well as decrease luminal pH [1].

Bacteria commonly used in probiotic formulations include lactobacilli, bifidobacteria, enterococci, streptococci and Bacillus clausii. Saccharomyces boulardii, live yeast, is also a probiotic and can be used in the treatment of recurrent C. difficile infection.

The Role of the Gut in Sepsis and the Surgical Patient

The epithelial barrier of the gastrointestinal tract is designed to prevent invasion of pathogens, but it is strongly influenced by the resident microflora. In a healthy gastrointestinal tract, the epithelial barrier still allows a degree of bacterial penetration, allowing the microflora to stimulate mucosal immune responses, which are usually mutually beneficial. Disruption or inflammation of the epithelial barrier can interrupt this relationship, lead to harmful mucosal immune responses that can result in further epithelial dysfunction, as well as allow bacterial translocation.

Key to the "gut origin of sepsis hypothesis" in surgical patients is the process of bacterial translocation, whereby the intestinal barrier is overcome and intestinal microflora can cross to the mesenteric lymph nodes and beyond, thus precipitating sepsis. In surgical patients, this may occur via a combination of increased epithelial barrier permeability, reduced gastrointestinal motility, bacterial overgrowth, changes in immune system regulation, as well as potential intestinal ischaemia and reduced nutrition around the time of surgery. Gatt *et al.,* there is evidence that intestinal obstruction, inflammatory bowel disease, jaundice, malignancy, pre-operative total parenteral nutrition, emergency surgery and gastric colonisation with microorganisms can be associated with increased bacterial translocation [2].

Deitch suggested that one of three pathophysiological conditions was necessary for bacterial translocation to occur [3]. These conditions comprised disruption of the intestinal microflora, impaired host immunity and loss of the mucosal barrier. More recently, Deitch proposed the "three hit model", comprising an event causing splanchnic hypoperfusion and local inflammation, then a reperfusion injury resulting in reduced gut barrier function and further local inflammation, followed by bacterial translocation and a further inflammatory reaction [3].

Potential Mechanisms of Probiotic Action in Surgical Patients

Probiotics have been shown to influence the function of the epithelial barrier in a variety of beneficial ways depending on the particular probiotic organisms. There is evidence that probiotics can potentially reduce bacterial translocation in a variety of ways. Firstly, they can physically reduce bacterial adhesion and translocation at the brush border via a competitive exclusion effect. They may act on toll-like receptors and induce the production of protective cytokines, reduce epithelial permeability changes and apoptosis mediated by inflammatory cytokines, maintain epithelial tight junction function and stimulate mucus gene expression [4]. Secondly, probiotics can exert a direct antimicrobial effect on other organisms by reducing luminal pH, inducing the production of defensins, secreting bacteriocins as well as inhibiting bacterial adhesion [5]. Thirdly, there is evidence that probiotics can influence the production of certain cytokines including the antiinflammatory cytokine IL-10 [6], as well as affect immune function by stimulating dendritic cells, which can in turn induce regulatory T-cell production.

Probiotics in Surgical Patients

When looking at the use of probiotics in surgical patients, it is helpful to try and group the studies by surgical condition or operation type to allow for a meaningful comparison.

Elective Abdominal Surgery

McNaught *et al.,* looked at the use of Lactobacillus plantarum 299v, given peri-operatively, in reducing the incidence of post-operative infectious complications and bacterial translocation in 129 patients undergoing elective abdominal surgery [7]. The authors found no significant difference in the frequency of post-operative infectious complications between treatment and control (12% vs. 14%), and no reduction in bacterial translocation in the probiotic group (12% vs. 12%), although there was no placebo or blinding in this study. A similar study using Lactobacilli post-operatively in 90 patients showed similar results [8]. The incidence of infections was the same in the treatment and placebo groups (10%), although the treatment group required antibiotics for a significantly shorter time (p ¼ 0.04).

Anderson *et al.,* looked at the use of peri-operative synbiotics vs. placebo in 137 patients undergoing elective abdominal surgery in a randomised double-blind study [9]. The authors found no significant difference in infectious complication (32% vs. 31%) or bacterial translocation rates (12.1% vs. 10.7%). Despite a more robust design, patient numbers were still small and the overall prevalence of bacterial translocation was also much lower than estimated. Therefore, the calculated sample size required was probably far too small, thus making the results difficult to interpret. However, the findings were in keeping with those of Horvat *et al.,* in a study investigating the use of synbiotics in 76 patients undergoing elective colorectal surgery [10]. However, other work involving 92 patients in a non-blinded study has suggested that pre-operative synbiotics can reduce the rate of bacterial translocation in patients undergoing elective colectomy ($p < 0.001$), although this did not translate into a reduction in septic episodes [11].

Hepatobiliary Surgery

There is some evidence that synbiotics may reduce infectious complications following elective surgery for biliary cancer. A non-blinded study involving 54 patients found that rates of infection were significantly lower with the post-operative use of synbiotics (19% vs. 52%, $p < 0.05$) [12]. Subsequent work, with a similar group of 101 participants, showed a significant reduction in post-operative infectious complications when synbiotics were given pre and post-operatively rather than just post-operatively (12.1% vs. 30.0%, $p < 0.05$) . This particular study was not blinded or placebo-controlled, but is interesting in terms of the timing of treatment, as it suggests that "priming" the bowel with synbiotics pre-operatively may confer additional benefits to those shown with postoperative synbiotics in these patients.

Patients undergoing liver transplantation have a particularly high risk of post-operative infectious complications. Not only is it a very substantial

operation, but the patients are often in a poor pre-operative condition, they are commenced on post-operative immunosuppressive agents and cirrhosis is also associated with relatively high levels of bacterial translocation. In a randomised placebo-controlled trial with 105 patients, synbiotics containing Lactobacillus plantarum 299 were shown to significantly reduce the rate of post-operative bacterial infections in liver transplantation compared to selective bowel decontamination (13% vs. 48%), whilst an inactivated preparation resulted in a much smaller reduction (34%) [13]. A further study by the same group (n ¼ 66) showed a significant reduction in infection rates with synbiotics compared to prebiotics alone (3% vs. 48%) [14], although it did not involve a placebo group.

Trauma

Many studies have investigated the use of prebiotics in the critical care environment, some of which have focused on patients with multiple injuries. This has often proved a difficult area to study, with criticisms highlighting difficulties in comparable product delivery, intolerance of the regimes, the common use of proton pump inhibitors, differences in feeding, poor nasogastric tube tolerance, gut stasis, aggressive antibiotic therapy, relative immunosuppression, as well as the complicating use of drugs such as opiates, sedatives and broad-spectrum antibiotics.

Trauma patients requiring treatment in an intensive care unit are at considerable risk of developing infections. A variety of factors can play a role in this, including the systemic inflammation involved, increased catabolism, reduced immune function, increased bacterial translocation in the gastrointestinal tract.

With regard to ventilated trauma patients, a doubleblind placebo-controlled trial looked at the use of synbiotics in 65 patients with some encouraging results [15]. The rate of infections, severe sepsis, length of stay on the intensive care unit, and the number of days with mechanical ventilation were all significantly reduced. Whilst not reaching statistical significance, patient mortality was also lower in the symbiotic group (14.3% compared to 30% in the placebo group, p ¼ 0.12). A further study by the same group showed a significant reduction in bacteraemia and ventilator- associated pneumonia (VAP) rates with synbiotic use [16].

Acute Pancreatitis

Acute pancreatitis is a serious condition with an incidence that continues to increase worldwide. It ranges from a mild, self-limiting illness to pancreatic necrosis and infected pancreatic necrosis with a mortality rate of up to 30%. Systemic antibiotic prophylaxis is used to prevent secondary infection in acute pancreatitis, despite two double-blind, placebo-controlled trials [17] and two meta-analyses that do not support this practice. It is thought that increased gut permeability and bacterial translocation are important factors in the development of infectious complications in these patients [18], so selective gut decontamination, whereby nonabsorbable antibiotics are given enterally in addition to intravenous antibiotics, has also been tried [19]. There was no significant reduction in mortality and supporting work is lacking, so the UK Working Party on Acute Pancreatitis does not recommend the use of this treatment.

The idea of increased gut permeability and bacterial translocation has also led to research into the potential use of probiotics in acute pancreatitis. The first of these studies was by a Hungarian group, looking at the use of probiotics in 50 patients with acute pancreatitis compared to an inactivated product [20]. All patients also had feeding via nasojejunal tubes. They found significantly lower rates of infected pancreatic necrosis requiring surgery in the probiotic group, although patients with biliary tract disease were excluded making it difficult to draw broad conclusions. A further randomised and doubleblind study by the same group involved 83 patients, including those with biliary tract disease, with synbiotics rather than probiotics [21]. There was a significant reduction in overall complications in the synbiotic group ($p < 0.05$), as well as the combined rate of Systemic Inflammatory Response Syndrome (SIRS) and multiple organ failure (8 vs. 14, $p < 0.05$), but there was no significant difference in mortality.

Much of the subsequent discussion has understandably focussed on the increased mortality rate in the probiotic group. With regard to methodology, the authors questioned whether the significantly larger numbers in this study enabled the detection of mortality differences and rare complications that may have been missed by the preceding studies. However, this does not explain the occurrence of these events. The most likely factor would seem to be the bowel ischaemia noted in the probiotic group.

Non-occlusive mesenteric ischaemia is recognised in both acute pancreatitis and critically ill patients [22]. Furthermore, enteral feeding can also be associated with bowel ischaemia in the critically ill. The probiotic group may therefore have been at high risk of this complication. The authors suggested that the probiotics may put an additional oxygen demand onto the bowel wall and possibly also induce inflammation of the enterocytes. These must indeed be possibilities, although any such effect was not cumulative as one might have expected.

The results of this study have understandably had a huge impact on this field of research. It is unlikely that there will be further work involving the use of probiotics in acute pancreatitis until we have a better

understanding of the processes that led to the results of the PROPATRIA study.

Meta-Analysis

A recent meta-analysis looked at the use of probiotics and synbiotics in abdominal surgery (excluding trauma and acute pancreatitis) [23]. Nine randomised controlled trials were included, with a total of 733 patients. The authors found that the incidence of infectious complications was significantly lower with prebiotics/synbiotics (OR 0.26, 95% CI 0.12–0.55), along with duration of antibiotic therapy and length of hospital stay. However, the incidence of post- operative wound infection, intraabdominal abscess formation and mortality was not significantly lowered. Again, the heterogeneity patients and trial design were noted as possible confounding factors in the meta-analysis. Regarding acute pancreatitis alone, a recent metaanalysis looked at a total of 559 patients across seven randomised studies (including small and non-English language) [20]. The authors found that there was no significant reduction in infectious complications or mortality with the use of pre-, pro- or synbiotics in acute pancreatitis, although length of hospital stay was significantly reduced.

CONCLUSIONS

The appeal of the potential use of probiotics in clinical medicine is clear. Although they are a varied group of products, they have been deemed safe for human consumption and exhibit beneficial properties when consumed. As well as the direct effects of their presence within the bowel lumen, they also display immunomodulatory attributes which have been of great interest to researchers.

This review has looked at the use of probiotics in surgery, a field in which most studies have focussed on reducing the incidence of infective complications. From the evidence that we have, meta-analysis suggests that probiotics/synbiotics may reduce infectious complications in abdominal surgery, as well as shorten the duration of antibiotic therapy and length of post-operative stay. However, surgical patients vary according to the particular condition or surgery involved, making it necessary to group the studies accordingly. Even the related trials often differ in methodological approach and in the probiotic preparations used. Many of the studies have been small in size and some have lacked placebo control or blinding. Also, some studies only gave the intervention post-operatively, whilst there is some suggestion that preoperative “priming” may confer additional benefits [17]. These factors can make interpretation of the current evidence difficult and further work is certainly required.

Looking at the different patients groups, patients undergoing hepatopancreatobiliary surgery seem to have lower rates of infectious complications with synbiotics and perhaps probiotics. This is often complex surgery, with significant risks of complications including infections, but is frequently elective and patients will not usually be in organ failure at the time of surgery (liver transplantation patients will vary in this aspect as they are a very heterogenous group, needing transplantation for a variety of reasons which may not be acute). The results are interesting in this context and it appears the most promising application of probiotics in surgery, although clearly further work is required. From the evidence that we have, ventilated trauma patients may also benefit from synbiotics, not only from a reduction in the incidence of infections and severe sepsis, but also duration of mechanical ventilation and duration of stay in critical care.

With regard to elective abdominal surgery and elective colectomy there is very little evidence of benefit with 96 Eur Surg 2/2012 © Springer-Verlag Probiotics in Surgery Review either probiotics or synbiotics. It may be that these studies were too small to detect a significant benefit, but the majority of the studies covered a wide range of pathology and surgery, making them difficult to interpret. Alternatively, it may be that an elective colectomy is less complex than hepatopancreatobiliary surgery and that the patients will potentially be less unwell in the postoperative period.

The most controversial and striking work has involved probiotics in acute pancreatitis. Following encouraging results from smaller studies, the PROPATRIA multi-centre trial produced markedly different findings. Not only was there no reduction in infectious complications, but also the mortality rate was significantly higher in the treatment group, where bowel ischaemia was a notable feature. The reasons for this are not entirely clear, but it is notable that non-occlusive mesenteric ischaemia is recognised in both acute pancreatitis and critically ill patients. It is quite possible that in a patient with acute pancreatitis, with a degree of bowel ischaemia and increased bowel wall permeability, high dose probiotics could cause a further enteropathy and further morbidity.

It should be noted that, as discussed above, results with ventilated trauma patients were encouraging. Despite these patients being critically ill and with a degree of organ failure, there were no such problems as with the acute pancreatitis cohort. It may be that the acute pancreatitis patients have an additional drive towards bowel ischaemia above that of a less specific critical illness, leaving them at greater risk to further damage.

There would appear to be potential for the use of probiotics in surgical patients, but it is clear that each particular type of surgery or condition needs to be considered separately and that probiotics may actually be harmful in certain circumstances. Certainly, as things stand, it would seem advisable that high-dose probiotics

should not be used in situations where the bowel wall may already be significantly ischaemic and hence permeable, such as in acute cases of pancreatitis. Large scales, well-designed trials, with pre-operative rather than just post-operative probiotics, are needed to advance our knowledge in this field. It would also be helpful to try and standardise such work with regard to the probiotics used and their dosage, so that they may be more comparable. With regard to acute pancreatitis, further research is necessary to determine the exact underlying mechanism behind the results from the PROPATRIA study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest. No funding or additional support was received for this work.

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