PROBIOTICS IN THE SURGICAL PATIENT

As antibiotic resistance increases, Dr Mayur Joshi looks at the use of probiotics to improve surgical outcomes and reduce post-operative infection.

Post-operative infections are the most common complication of surgery and continue to represent a substantial problem, both in terms of clinical burden and financial cost. As a result, peri-operative antibiotic use is widespread and antibiotic resistance is increasingly becoming a significant concern to the healthcare industry. With this in mind, alternative methods of improving surgical outcomes are being investigated; the fact that post-operative infections and sepsis are commonly caused by the patient's own intestinal bacteria, or microflora, (via bacterial translocation) represents an interesting starting point[1].

The gut microflora plays an important role in the body's defence against pathogens and the relationship between the microflora of the gastrointestinal (GI) tract and its function is well documented[2]. Together they form the first line of defence against pathogens and in fact the gut bacterial population also has effects on the systemic immune system as well as local effects on immune tissue within the GI tract[3]. Indeed it has been postulated that we are 200,000 times more prone to infection than if without our microflora[4].

The gut origin of sepsis theory states that bacteria that usually inhabit the GI tract are able to pass into extra-luminal areas and cause sepsis at distant sites[5]. Among the main causes is disruption of the gut barrier, increased intestinal permeability, gut microbial imbalance, and immunologic compromise of the host and then subsequent 'translocation' of bacteria[6]. Bacterial translocation has been shown to be associated with an increased risk of septic complications[5] illustrating the importance of the gut microflora and its relationship with intestinal barrier function.

There is substantial evidence to suggest that surgical trauma in itself disrupts the gut microflora and its function, in turn disrupting metabolism and immune function without the need for bacterial translocation[7]. Furthermore, altered nutritional states, use of peri-operative antibiotics, on-going disease processes and other pharmacological interventions will also alter gut microbiome function[8]. It stands to reason that peri-operative optimisation of the gut bacterial population should proffer beneficial effects on surgical outcomes, specifically on infectious complications of surgery.

PROBIOTICS

Probiotic supplements, therefore, represent a potential therapeutic strategy to help optimise the microflora of the gut prior to, during and after elective surgery. The accepted definition of a probiotic is a live microorganism that, when administered in adequate amounts, confers a health benefit on the host[9].

The beneficial effects of probiotics have been documented for over a century now, initially through anecdotal evidence but now, increasingly, through rigid scientific study and clinical trial work. In recent years the volume of research being carried out and published has increased massively. This includes the potential for probiotics to be used within a general surgical unit in the hospital setting.

Multiple mechanisms of action of probiotics have been postulated and indeed identified as to how these living organisms produce their beneficial effects at a local and systemic level. The overall concept is based on redressing imbalance within the gut, displacing pathogenic bacteria with beneficial species.

The way they achieve this is through a number of mechanisms that have been summarised in the table below:

Antimicrobial Properties	Barrier Function Enhancement	Immunomodulation
• Lowers luminal pH • Production of bacteriocins • Inhibit bacterial adhesion • Inhibit baterial invasion	• Increase mucus production • Enhance barrier integrity	• Direct effects on epithelial cells • Effects on dendritive cells • Effects on monocytes/ macrophages • Effects on lymphocytes

(Adapted from Ng et al[10])

Not all probiotic strains will possess all of the above properties (and indeed this overview does not represent the full spectrum of properties) but it serves to demonstrate how they are able to displace pathogenic bacteria in the gut using multiple mechanisms of action before exerting their local and systemic effects on barrier function and immune modulation. In addition, it is thought that different strains of probiotic bacteria work synergistically to exert a greater effect than a single strain, resulting in much improved clinical outcomes when using a multi-strain formulation[11]. This trend has been demonstrated right the way through scientific study of probiotics; from in vitro studies to animal models and human clinical trials the use of a multi-strain probiotic formulation has been shown to be advantageous[12].

EVIDENCE BASE

There have been several studies looking at the use of probiotics peri-operatively with some encouraging results. In particular, probiotics used in hepatopancreatobiliary surgery, in particular liver transplantation, have shown some good results and this is where we start our review of the literature.

Hepatic transplant surgery is associated with a high rate of bacterial infection in the early post-operative period with reported rates between 30% and 86%[13]. These infective complications are associated with longer hospital stay, prolonged antibiotic use, graft loss and increased morbidity and mortality. Immunosuppressive medication and general poor nutrition in these patients also contribute to the high bacteraemia rates seen in this type of surgery. These factors will all contribute to a dysbiosis of the gut microflora making them potentially excellent candidates for probiotics use.

One study looked at the use of probiotics in major abdominal surgery[14]. The conventional post-operative feeding protocol in the hospital was total parenteral feeding for the first five days followed by introduction of oral fluids until normal diet resumed on day nine; this was compared with a second group who received early enteral feeding with fibre plus a probiotic and finally a third control group that received fibre and a placebo. Patients in the probiotic group had significantly reduced infectious complications (10%) compared to the conventional group (30%) and shorter duration of antibiotic use.

In fact the same group has looked repeatedly at the use of probiotics in other hepatobiliary procedures with similarly impressive results. Later in 2002 they looked at patients undergoing liver transplantation in a randomised placebo controlled trial[15]. Once again there were three groups this time all receiving early enteral feeding; group A also received selective bowel decontamination (SBD), group B received enteral feed with fibre plus a probiotic whilst group C received fibre plus heat killed probiotic. The probiotic group developed significantly fewer post-operative bacterial infections (13%) than both the SBD group (48%) and inactivated probiotic group (34%).

They continued their research in 2005 again looking at liver transplant patients but this time comparing early enteral feeding, including a multi-strain probiotic formulation given with fibre, against a control group[13]. Post-operative infection rates were massively reduced in the probiotic group (3%) when compared to the control (48%). In addition the duration of antibiotic use was significantly reduced in the probiotic group.

In the final study of their series, Rayes' group looked at the use of probiotics after pylorus-preserving pacreatoduodenectomy or PPPD[16]. This surgery is mainly performed for cancerous tumours of the head of the pancreas and structurally related organs (biliary tree, duodenum). Once again all patients received early enteral feeding with one group receiving a multi-strain probiotic formulation whilst the other group received placebo. They found that the incidence of bacterial infections post-operatively was greatly reduced in the probiotic group (12.5%) compared to the control (40%).

The use of probiotics has also been studied in operations involving the distal GI tract and these impressive results were reproduced in a trial looking at the maintenance of remission in patients with ulcerative colitis who had undergone colonic resection and formation of an ileo-anal pouch[17]. These patients will invariably develop pouchitis (inflammation of the ileal reservoir) and most within their first post-operative year[18]. The aetiology is not well understood but the theory that faecal stasis and bacterial overgrowth play a major role is supported by the fact that the mainstay of treatment, antibiotics, achieves excellent clinical results[19].

The group looked at the maintenance of clinical, endoscopic and histologically proven remission in patients with previous pouchitis, comparing a probiotic group with a group taking a placebo. 100% of the placebo group relapsed within the course of the study (which was set at nine months). In the probiotic group 85% were still in remission at the end of the study. Interestingly, all of these patients

subsequently relapsed within four months of suspension of probiotic supplementation. Significantly, a probiotic has been found to be just as effective as mesalazine, the gold standard of treatment, at maintaining remission in patients with ulcerative coilitis[20].

DISCUSSION

These trials demonstrate that there is huge potential for the use of probiotics in the management of surgical patients but there is clearly further work to be done. The studies are not necessarily comparable as they do not use the same probiotic formulation across the board; this will invariably lead to a heterogeneity of properties which is likely why probiotic mixtures have been shown to be more effective. This heterogeneity between trials will also likely explain the variability in results seen in other studies.

Multi strain probiotic formulations will possess a greater range of mechanism of actions and, therefore, a potentially greater range of properties. In addition, they are likely to work synergistically to potentiate or enhance each other's beneficial effects as they have been shown to work better as a mixture compared to the individual component strains of that mixture[11].

Another consideration is that whilst the evidence is excellent and overwhelmingly positive for patients undergoing elective surgery, the evidence in acute surgical conditions and emergency surgery is less conclusive. There has been much evidence to support the use of probiotics in the management of acute pancreatitis[21] but there has also been evidence to suggest that use of probiotics in these patients has a detrimental effect on clinical outcome[22]. Despite this trial, the safety of probiotics has been well established and the use of multi-strain probiotics in the elective surgical setting is highly promising and with further trials we could see their use enter mainstream clinical practice.

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REFERENCES

1. Guarner F, Malagelada JR. Gut flora in health and disease. *Lancet* 2003;361:512-9.
2. Holzapfel WH , Haberer P, Snel J, Schillinger U, Huis in't Veld JH Overview of gut flora and probiotics. *International Journal of Food Microbiology* 41 (1998) 85–101
3. Tlaskalová-Hogenová H, Stepánková R, Hudcovic T, Tucková L, Cukrowskab B, et al. Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. *Immunology Letters* 93 (2004) 97–108
4. Collins FM, Carter PB. 1978. Growth of salmonellae in orally infected germfree mice. *Infect Immun.* Jul;21(1):41-7.
5. MacFie J, O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P. Small intestine:Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. *Gut* 1999;45:2 223-228 doi:10.1136/gut.45.2.223
6. Correia MI, Liboredo J, Consoli M. The role of probiotics in gastrointestinal surgery. *Nutrition* 28 (2012) 230–234
7. Hartman AL, Lough DM, Barupal DK, et al. Human gut microbiome adopts an alternative state following small bowel transplantation. *Proc Natl Acad Sci U S A.* 2009;106(40):17187-17192. in *Food.* London: Ontario (Canada); 2002.
8. Jakobsson HE, Jernberg C, Andersson AF, Sjolund-Karlsson M, Jansson JK, Engstrand L. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS ONE.* 2010;5(3):e9836.
9. FAO/WHO Expert Consultation. *Guidelines for the Evaluation of Probiotics*
10. Ng, S.C., Hart, A.L., Kamm, M.A., Stagg, A.J. and Knight, S.C. (2009), Mechanisms of action of probiotics: Recent advances. *Inflamm Bowel Dis*, 15: 300–310. doi: 10.1002/ibd.20602
11. Chapman CM, Gibson GR, Rowland I. (2011) Health benefits of probiotics: are mixtures more effective than single strains? *Eur J Nutr.* 2011 Feb;50(1):1-17
12. Timmerman HM, Koning CJ, Mulder L, Rombouts FM, Beynen AC (2004) Monostrain, multistrain and multispecies probiotics--A comparison of functionality and efficacy. *Int J Food Microbiol.* 2004 Nov 15;96(3):219-33.
13. Rayes N, Seehofer D, Theruvath T, Schiller RA, Langrehr JM, Jonas S, et al. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantationda randomized, double-blind trial. *Am J Transplant* 2005;5:125–30.
14. Rayes N, Hansen S, Seehofer D, Muller AR, Serke S, Bengmark S, et al. Early enteral supply of fiber and Lactobacilli versus conventional nutrition: a controlled trial in patients with major abdominal surgery. *Nutrition* 2002;18:609–15.
15. Rayes N, Seehofer D, Hansen S, Boucsein K, Muller AR, Serke S, et al. Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. *Transplantation* 2002;74:123–7
16. Rayes N, Seehofer D, Theruvath T, Mogl M, Langrehr JM, Nussler NC, et al. Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: a randomized, double-blind trial. *Ann Surg* 2007;246:36–41.
17. Gionchetti P, Amadini C, Rizzello F, Venturi A, Poggioli G, Campieri M. Probiotics for the treatment of postoperative complications following intestinal surgery. Best practice & research. *Clinical gastroenterology* 1 October 2003 (volume 17 issue 5 Pages 821-831)
18. Stahlberg D, Gullberg K, Liljeqvist L et al. Pouchitis following pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk and risk factors. *Diseases of the Colon and Rectum* 1996; 39: 1012–1018.
19. Shepherd NA, Hulten L, Tytgat GNJ et al. Workshop: pouchitis. *International Journal of Colorectal Disease* 1989; 4: 205–229.
20. Kruis W, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. *Gut.* 2004 Nov;53(11):1617-23.
21. Olah A, Belagyi T, Issekutz A, Gamal ME, Bengmark S (2002) Randomized clinical trial of specific Lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. *Br J Surg* 89:1103–1107
22. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008 Feb 23;371(9613):651-9. doi: 10.1016/S0140-6736(08)60207-X. Epub 2008 Feb 14.