Original Paper

Synbiotic Control of Inflammation and Infection in Severe Acute Pancreatitis: a Prospective, Randomized, Double Blind Study

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ABBREVIATIONS:
Colony Forming Unit (CFU); Multiorgan Failure (MOF); Systemic Inflammatory Response Syndrome (SIRS); Lactic Acid Bacteria (LAB); Acute Pancreatitis (AP); Fine Needle Aspiration (FNA)

ABSTRACT

Background/Aims: Experimental and clinical studies demonstrated that probiotics containing lactobacilli significantly improve the outcome of acute pancreatitis. In a prospective, randomized, double-blinded study the role of "Synbiotic 2000", a new synbiotic composition with high colony forming unit (CFU) was evaluated in the treatment of severe acute pancreatitis.

Methodology: Patients with severe acute pancreatitis were randomized into two groups. Nasojejunal feeding was commenced within 24 hours after admission in both groups and continued for at least seven days. The first group of patients received four different lactobacilli preparations with 10^{10} CFU, respectively, and prebiotics containing four bioactive fibers (inulin, beta-glucan, resistant starch and pectin) in addition. Patients in the second (control) group received only prebiotics.

Results: 62 patients with severe acute pancreatitis completed the study. Altogether 8 patients died. Lower incidence of multiorgan failure (MOF), septic complications and mortality were detected in the first group compared to the control, but the differences were not significant statistically. The total incidence of systemic inflammatory response syndrome (SIRS) and MOF were significantly different between the two groups (8 *vs.* 14; $p<0.05$). Furthermore, the number patients recovering with complications were significantly less in the first group receiving modern synbiotic therapy compared to the control ($p<0.05$). Finally, lower rate of late (over 48 hours) organ failure was detected in the first *versus* the control group (3.0% *vs.* 17.2%).

Conclusions: The results suggest that early nasojejunal feeding with synbiotics may prevent organ dysfunctions in the late phase of severe acute pancreatitis. In addition, the data also indicate that the infection of pancreatic necrosis may be associated with early phase organ failure.

INTRODUCTION

The premorbid health status of the individual affected by severe acute disease such as severe acute pancreatitis is of outmost importance for outcome. Important early risk factors and determinants of poor outcome are in addition to pre-morbid health status high age and body mass index (1,2). Even if the lesion in its very early stage is restricted to the acinar cells of pancreas, it will within hours, if not minutes, spill over to the gut, the home of about 80% of the immune system, and thereafter soon to the rest of the body, especially the chest. Extensive deterioration of the immune system paves the way for subsequent complications and poor outcome. An exaggerated and prolonged inflammation, a superinflammation, which involves distant organs, referred to as system inflammatory reaction (SIR), provides an important early warning. An early "cytokine storm" (3-5) and signs of deterioration of immune functions such as suppression of expression of monocyte histocompatibility leukocyte antigen (HLA)-DR are strongly associated with subsequent development of septic complications and poor outcome (5-7). Important ingredients in the progress of disease, and determinants for poor outcome, are degree of oxidative stress, neutrophil activation and neutrophil infiltration of tissues, preferably the lungs (8). Recent information suggests that antigens, most likely of intestinal origin, fuel the inflammatory response by activating T-cells (9). It is to a large extent the lungs, which are the target of early (within 24 hrs) superinflammation and single organ failure [91% (10), 81% (11)], but impairment of renal function [4,5% (10), 5% (11)] and coagulation [4,5% (10), 14% (11)] are also seen in the early phase of disease.

The most effective tool to reconstitute the body's resistance to disease and prevent further deterioration of the immune system/minimize progress of disease, is

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early and aggressive enteral nutrition. A recent meta-analysis based on six randomized controlled trials reports compared to parenteral nutrition lower incidence of infections (relative risk 0.45, 95% confidence interval 0.26-0.78, $p=0.004$), reduced surgical interventions (0.48, 0.22-1.0, $p=0.05$) and reduced length of hospital stay (mean reduction 2.9 days, 1.6-4.3 days, $p<0.001$), but no significant differences observed in mortality (0.66, 0.32-1.37, $p=0.3$) or non-infectious complications (0.61, 0.31-1.22, $p=0.16$) (12).

However, much support that it is more the content of the enterally supplied nutrition than the mode of administration *per se*, which is important for enforcing resistance to further deterioration of disease. Experimental evidence supports that supply of LAB to animals with induced sepsis will prevent infiltration of lung tissue with neutrophils, reduce the increases in myeloperoxidase and malonaldehyde activity in the lungs and destruction of lung tissue (Ilkgul O *et al.*, personal communication). Potent lactic acid bacteria and bioactive plant-derived fibers has the potential to enforce the innate but also to some extent the acquired immune system (13,14).

We did in a previous study compare daily supplementation of 1 billion live *Lb plantarum 299* (LL299) with 1 billion heat-killed *Lb plantarum 299* (HL299), plus in both groups 10g of oat fibers. Infected pancreatic necrosis and abscesses were seen in 1/22 (4.5%) of patients supplied LL299 *vs.* 7/23 (30%) of those supplied HL299 ($p=0.023$) (15). Subsequent letters to the Editor suggested methodological frailties including no pre-study power calculation, no defined primary endpoint and lack of analysis by intention to treat and doubtful data analyses (16,17). However, the fact that similar observations are made in other groups of patients: after extensive operations such as liver transplantation (18-20) and in trauma patients (Kompan L *et al.*, personal communication) supports that the observation that significant prevention of inflammation and infection can be expected from prophylactic enteral nutrition containing synbiotics.

Although the above study was able to significantly reduce the incidence of infected pancreatic necroses, it did not prevent development of SIRS (6 *vs.* 2) and MODS (2 *vs.* 2). If anything a tendency towards increase in SIRS was observed. The present study was undertaken as an attempt to investigate if use of a composition consisting of several lactic acid bacteria (LAB) and bioactive fibers and a much larger dose of LAB (40 billion) has the capacity to reduce also the incidence of SIRS and MODs. Special attempts were made to focus mainly on patients with severe acute pancreatitis.

METHODOLOGY

Patients admitted with acute pancreatitis (AP) to the Surgical Department of the Petz Aladár Teaching Hospital in Gyur between July 1st 2001 and July 1st 2004 were enrolled in the study. Inclusion criteria were: typical clinical picture including abdominal pain, serum amylase elevation (over 200 U/L, normal value: 70 U/L), and onset of symptoms less than 48 hours prior to admission.

In contrast to our previous prospective study, patients with biliary etiology were also included in the trial. Patients with an acute exacerbation of chronic pancreatitis were not included. Attempts were made to only include cases of severe pancreatitis. As the progress of disease during the first 24-48 hours is difficult to assess, all patients presenting with typical clinical symptoms and laboratory signs of AP were on admission randomized and provisionally included in the trial, altogether 83 patients. Forty-eight hours later the Imrie score (= or >3), CRP values (>150mg/L), and when indicated, use of contrast-enhanced computer tomography (necrosis > 30%) were used to evaluate the extent of pancreatic necrosis and severity of disease, and only patients regarded as severe included in the study. At this stage 17/83 patients did not meet these criteria and were consequently excluded. Excluded were also three patients, who did not tolerate jejunal feeding and one patient who repeatedly removed the feeding tube. The nasojejunal tube (Angiomed duodenal set, Germany; caliber 14Fr and length 150cm) was inserted and positioned by radiography. Feeding was in all cases instituted on the day of arrival and continued for a minimum of 7 days. All patients received from the first day enteral nutrition through a nasojejunal tube and gravity-driven continuous drop a nutrition solution containing fiber, Nutrition Fibre (Nutricia, Amsterdam, The Netherlands). The dose was during the following 2-3 days gradually increased reaching its optimum within 2-3 days, when usually the goal to supply 30kcal/kg body weight was reached.

On admission, and after consent was obtained, the patients were randomized into one of the following two groups.

Group A: Enteral feeding with a multi-strain/multi-fiber synbiotic: Synbiotic 2000™. It consists of a mixture of four LAB, one from each of the four main genera of lactobacillus; 10^{10} of *Pediacoccus pentosaceus* 5-33:3, 10^{10} of *Leuconostoc mesenteroides* 32-77:1,10^{10} of *Lactobacillus paracasei* subsp *paracasei* 19 and 10^{10} of *Lactobacillus plantarum* 2362, e.g. 40 billion LAB per dose, plus a mixture of four well studied bioactive plant fibers: 2.5g betaglucan, 2.5g inulin, 2.5g pectin and 2.5g resistant starch, totally 10g plant fibers. The composition was constructed after extensive studies of >350 human and >180 plant strains by Lund university microbiologist Åsa Ljungh and her team (21,22). The LAB to be used in the composition were chosen on documented ability of the LAB to produce bioactive proteins, transcribe NF-κB, produce pro- and anti-inflammatory cytokines, produce antioxidants, and to complement each other's functions. All four LAB have somewhat different functional characteristics, but show synergistic effects when supplemented together. Synbiotic 2000 is produced by Medipharm, Kågeröd Sweden and Des Moines, Iowa, USA.

Group B: Enteral feeding with the same bioactive

plant fibers as in Synbiotic 2000, but no LAB added e.g. 2.5g betaglucan, 2.5g inulin, 2.5g pectin and 2.5g resistant starch, totally 10g plant fibers. With this only difference the patients were treated identically to that in group A.

Numbered sachets with content of either active Synbiotic 2000 or only fibers were provided and after randomization blindly administered daily to the patients for a period of 7 days minimum. Antibiotics were administered only in cases of suspected or manifest pancreatic infection or in severe complications such as organ failure. Septic complications, e.g. infected necrosis were initially treated with imipenem + cilastatin (Tienam, MSD) and following culture and sensitivity analysis antibiotics were given in accordance with recommendations.

In addition to routine laboratory studies procalcitonin levels (PCT-Q quick test, BRAHMS GmbH) and CT scans were performed on admission, on the 2-3rd and after 7-10th days. Bacterial infection of the necrosis was detected with assistance of CT or ultrasound-guided fine needle aspiration (FNA), or through direct samples from the pancreatic tissue if laparotomy was performed. FNA examinations were performed when bacterial infection was suspected by clinical signs (fever, WBC elevation, catabolism disorders, deteriorating general condition, early signs of organ dysfunction).

Data were analyzed using the Mann-Whitney, chi-square, and Fisher tests. A $p<0.05$ value was considered statistically significant.

TABLE 1 Characteristics of the Patient Material

	Group A (n: 33)	Group B (n: 29)	
Mean age (range)	47.5 (19-78)	46.0 (20-81)	NS Sex (male:female)
	27:6	25:4	NS
Etiology (alcoholic/other)	20/13	16/13	NS
Mean CRP level (sd)	216.7 (±98.6)	191.2 (±115.0)	NS
Mean Imrie score (sd)	2.9 (±1.2)	3.1 (±1.5)	NS
Rate of necrotic forms	20/33	18/29	NS

TABLE 2 Clinical Results

	Group A (n: 33)	Group B (n: 29)	
Total number of infections (n=)	9	15	
Chest infections (n=)	2	4	
Urinary tract infections (n=)	3	3	
Pancreas related infections (n=)	4	8	
Pancreatic abscesses	2	2	
Infected pancreatic necrosis	2	6	
SIRS (%)	3 (9)	5 (17.2)	
MOF (%)	5 (15.1)	9 (31.0)	
SIRS + MOF	8	14	$p<0.05$
Late (>48h) MOF (%)	1 (3.0)	5 (17.2)	
Complicated / uncomplicated cases	9/24	15/14	$p<0.05$
Surgery or drainage (%)	4 (12.1)	7 (24.1)	
Mean hospital stay (day)	14.9	19.7	
Exit (%)	2 (6.0)	6 (20.7)	

TABLE 3 Isolated Microorganisms

	Group A (n: 33)	Group B (n: 29)
Pseudomonas aeruginosa	1	4
Enterococcus faecalis	1	2
Enterobacter spp	1	1
Streptococcus spp	2	-
Staphylococcus aureus	1	1
Candida spp	-	2
Staphylococcus haemolyticus	-	1
Serratia spp	-	2
Klebsiella spp	-	1
Enterococcus faecium	1	-
Escherichia coli	-	1
Stenotrophomonas maltophilia	-	1
Citrobacter freundii	-	1
Total:	7	17

RESULTS

62 patients completed the trial and were further analyzed: 33 in group A and 29 patients in group B. There were no significant differences between the two groups with regard to age, sex and etiology of disease **(Table 1)**. The two groups were also comparable regarding CRP values, the Imrie-score, and the proportion of cases with necrosis as reflected by computer tomography **(Table 1)**.

Table 2 summarizes also the outcome in the two groups: the complications observed required interventions (operations and drainage), average length of hospital stay and the mortality rates. A significant reduction in rate of complications is observed in the synbiotic treated group ($p=0.049$). Multiorgan failure occurred twice as often in the control group, but this difference is not statistically significant. ($p=0.136$). However, when the cases of SIRS are added to the cases of MOF the difference becomes statistically significant in favor of synbiotic treatment ($p=0.048$). It was also observed that late MOF (later than 48 hrs) rarely occurred in the synbiotic treated group. However, due to the small size of material this difference was only marginal to significance ($p=0.089$).

Septic complications **(Table 3)** to pancreatitis (infected necrosis or pancreatic abscess), occurred less than half as often in the synbiotic treated group compared to the control group (12.1% *vs.* 27.6%), but due to the size of material was not statistically significant ($p=0.124$). The number of surgical interventions was also cut to half in the synbiotic treated group (12.1% *vs.* 24.1%).

The mortality rate was less than 1/3 in the synbiotic treated group (6.0% *vs.* 20.7%), but again due to the size of the difference did not reach statistical significance ($p=0.131$). Of the 8 lost patients, only 2 died within the first week: one patient in the synbiotic treated group on day 2 and one patient in the only fiber group on day 3. Six patients deceased late, on average on the 37th day (8th, 9th, 42nd, 49th, 55th and 57th days. Of these five only were fiber-treated and one synbiotic-treated (dead on the 55th day). Six

TABLE 4 The Total Number of Cases was 22 and 23 at Study 1, and 33 and 29 at Study 2 for Synbiotic and Control Groups

Feature	Study #pos	Exp #pos	Contr	Pooled estimate for RR and CI limits RR	CI (L)	CI (H)
MOF	I	2	2	0.5827	0.2483	1.3671
	II	5	9		(p=0.21)	
Abscesses	I	0	3	0.4213	0.0949	1.8696
	II	2	2		(p=0.26)	
Infected	I	1	4	0.2809	0.0817	0.9662
Necroses	II	2	6		(p=0.044)	
Sept compl.	I	1	7	0.3102	0.1197	0.8034
	II	4	8		(p=0.016)	
Surgical	I	1	7	0.3333	0.1269	0.8749
interventions	II	4	7		(p=0.026)	
Death	I	1	2	0.3468	0.0981	1.2255
	II	2	6		(p=0.10)	

of the deceased 8 patients had significant symptoms of MOF already during the first 48 hours with rapidly progressive respiratory and cardiovascular insufficiency, and in two cases also renal insufficiency.

DISCUSSION

The patient population was slightly larger in this study compared to our previous study, 62 *vs.* 45 patients. The severity of disease was also slightly higher in this study (Apache II Scores: Synbiotic treated 11.7±1.9, Controls 10.4±1.5) compared to the previous study (Apache II scores Synbiotic treated 8.9±1.6, Controls 9.4±2.3). This study demonstrates, as did our previous study, statistically significant advantages of synbiotic treatment in severe acute pancreatitis with large reduction in total number of infections and in number of infected pancreatic necroses. Both studies demonstrate, in addition obvious improvement in rate of total complications, surgical interventions and mortality, hospital stay, ICU stay, but without reaching the level of statistical significance.

Clearly, both studies suffer the disadvantages of having too small a patient population. Of that reason did we perform a meta-analysis based on both studies. Six different aspects were analyzed and, altogether six different aspects of synbiotic therapy were studied. When 18 RR (relative risk) values (6 and 6 out of study 1 and 2, plus 6 pooled estimates) were calculated only one (RR for MOF in study 1) was higher than 1.0, the other 17 values were shown to be below. However, when pooled together, the RR values are well below 1.0 for all the six examined aspects **(Table 4)**. The highest calculated RR was 0.58 (MOF), all the others were around or below 0.4, suggesting a 2 to 3 times better outcome of synbiotic therapy compared to the controls. Three of the parameters: infected necrosis, septic complications and surgical interventions were significant at the $p<0.05$ level: the total ranges of the 95% confidence intervals were below 1.0 **(Figure 1)**. The other three parameters: rate of MOF, abscesses, and deaths did not reach statistical significance. The total rate of septic complications (the sum of all the pancreatitis-related infections) demonstrated a statistically significant lower incidence of infection in the patients on synbiotic therapy compared with those receiving only fibers but no live LAB **(Figure 2)**.

The observed effects of synbiotic therapy are in line with observations made on other indications. Rayes *et al.* used the same formulation in a randomized study in human liver transplantation (23). Either Synbiotic 2000 or only fibers were provided from the day before surgery and during the first 14 postoperative days. The incidence of postoperative bacterial infections was significantly reduced; being 48% with only fibers and 3% with live LAB and fibers. In addition, the duration of antibiotic therapy was significantly shorter in the latter group.

A significant reduction of the commensal flora occurs early in the development of acute pancreatitis, most likely due to both the stress of disease and pharmaceutical treatment. It is observed in experimental pancreatitis that anaerobic bacteria and lactobacilli are significantly reduced within 6-12 hours after induction both in the distal small bowel and in the colon. These changes are almost instantly followed by significant overgrowth with potentially pathogenic microorganisms (PPMs) such as *E. coli*, and a dramatic increases in mucosal barrier permeability (lumen to blood) and in endothelial permeability (blood to tissue) (24,25), associated with increased

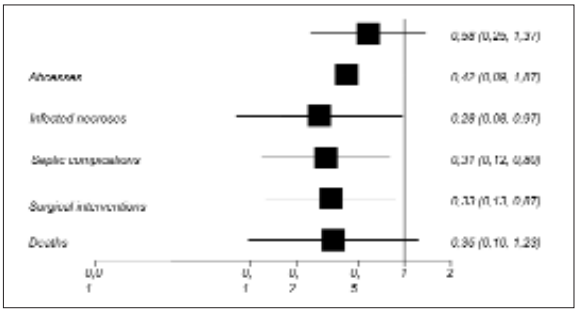

FIGURE 1 Risk of multiorgan failure, abscesses, infected necrosis, all septic complications, surgical interventions and mortality; results from meta-analyses of two randomized trials comparing synbiotic therapy with control (fibers only) in pancreatitis. Fix effects model of relative risk (95% confidence interval).

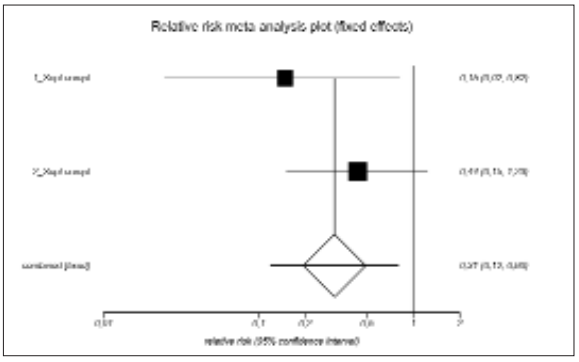

FIGURE 2 Relative risk of pancreatitis related septic complications.

microbial translocation, and microbial growth in mesenteric lymph nodes and pancreatic tissue (26).

To protect and enforce the body's immune functions and its ability to resist progress of disease is important. It is known that administration of antibiotics suppresses various immune functions and especially macrophage activities such as chemiluminescence response, chemotactic motility, bactericidal and cytostatic ability (27,28). This is so with standard supply and most likely even worse with selective digestive tract decontamination. Routine antibiotic prophylaxis in acute pancreatitis is also shown to be of no benefit (29).

In contrast to antibiotic treatment does synbiotic treatment preserve and even restore immune functions, reduce overinflammation and increase the body's resistance to further progress of disease. Experimental data, both unpublished (personal communication Ilkgul O, 2005) and published (30) demonstrate significant ability of the LAB used in the synbiotic composition to prevent neutrophil infiltration in the chest, subsequent tissue destruction, organ failure and progress of disease.

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