

Vloga sinbiotikov v zmanjšanju okužb po operacijah zloma v predelu kolčnega sklepa: pilotska študija

Role of synbiotics in reducing postoperative infections in patients with hip fracture: pilot study

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Izvleček

Namen: Število bolnikov z zlomom v predelu kolčnega sklepa narašča skupaj s staranjem prebivalstva. Okužbe, ki nastopajo po samem posegu, tako sistemske kot lokalne, pomembno vplivajo na uspeh operacije. Uporaba probiotikov dokazano zmanjšuje okužbe, zato nas zanima, ali lahko uporaba le-teh zmanjšuje okužbe tudi v skupini bolnikov po operacijah zlomov v predelu kolčnega sklepa.

Metode: Opravili smo dvojno slepo randomizirano študijo pri 51 bolnikih. Ob sprejemu so dobili ali preparat SYNBIOTIK 2000 FORTE ali placebo. Opazovali smo nastanek okužb, merili vrednost C reaktivnega proteina in opazovali, kako so bolniki prenašali uživanje preparata.

Rezultati: Okužbe so se pojavile pri štirih bolnikih v vsaki skupini. Pri sedmih bolnikih je šlo za uroinfekt in pri enem za okužbo rane.

Abstract

Purpose: Despite the development of surgical methods, infections continue to be serious postoperative complications. Probiotics have been shown to be effective in reducing the prevalence of infections. We explored the effectiveness of probiotics in reducing the prevalence of infections in subjects undergoing surgery for hip fractures.

Methods: Fifty-one patients admitted for surgical treatment of hip fractures were divided randomly into two groups: Synbiotic 2000 Forte and placebo. The occurrence of infection was closely observed upon hospital admission until the fifth postoperative day using, among other parameters, the C-reactive protein (CRP) level. Additionally, the patients' tolerance to Synbiotic 2000 Forte was established using subjective (self-reported problems) and objective means.

Zaključek: V raziskavi nismo dokazali vpliva SYNBIOTICA 2000 FORTE na zmanjševanje okužb po operacijah zlomov v predelu kolčnega sklepa. Število bolnikov bi moralo biti večje, skupina bi morala biti manj heterogena glede na stopnjo ogroženosti bolnikov pred operacijo in na čas med poškodbo in operacijo.

Results: Infection was confirmed in 4 patients in each group. Urinary tract infection was noted in 7 subjects and a local wound infection in 1 patient. No differences were found in CRP levels upon hospital admission and the fifth postoperative day. Tolerance to Synbiotic 2000 Forte was lower in patients undergoing placebo treatment. **Conclusion:** Synbiotic 2000 Forte did not reduce the number of postoperative infections. Further studies are needed to confirm these findings.

INTRODUCTION

Hip fractures are the most common reason for hospitalization on the trauma ward (1). Surgical treatment of hip fractures is linked to systemic and local infections (2). Treatment of infection can prolong the duration of hospitalization and significantly increases costs (1). The prevalence of mortality in patients affected by hospital-acquired infections can be appreciable.

Probiotics (living bacteria) can influence all three pathogenic mechanisms of bacterial translocation. They increase intestinal motility; stabilize the intestinal barrier (feeding of enterocytes, production of omega-3 fatty acids, stimulation of mucus secretion) (3); and enhance the innate immune system (induction of production of interleukin (IL)10, inhibition of the generation of T-helper-1 cells by dendritic cells (4), activation of macrophages, stimulation of secretory IgA and neutrophils with reduction of inflammatory cytokines (5)). By carrying the lactobacillus within the body we can reduce the risk of bacterial invasion, regulate the immune response, and thus reduce the chance of infection (6, 7, 8, 9).

Prebiotics (fibers) have important functions within the body. They are essential for: maintaining the growth

and function of the mucosa; maintaining water and electrolyte balance; providing energy and nutrients for the host and flora; enforcing the body's resistance against invading pathogens; stimulating growth (3).

The aim of the present study was to ascertain the influence of taking the preparation Synbiotic 2000 Forte (Medipharm, Stockholm, Sweden) upon the reduction of the prevalence of infections after surgery for hip fractures.

MATERIALS AND METHODS

The protocol for this randomized, double-blind study was approved by the Ethics Committee of Slovenia. Written informed consent was obtained from all subjects.

Fifty-one subjects undergoing surgery for hip fractures comprised the study group. They were randomized them into two groups: A (Synbiotic 2000 Forte) and B (placebo). The preparations were placed in identical-looking small bags.

The synbiotic preparation (Synbiotic 2000 Forte; group A) comprised a combination of 1011 colony-

Table 1: ASA classification for assessing physical status

| | |
|---------|---|
| Class 1 | Generally healthy, localized pathologic process |
| Class 2 | Stable mild-to-moderate systemic condition |
| Class 3 | Moderately severe systemic disorder |
| Class 4 | Severe and clearly life-threatening disorder |

Table 2: AO classification of hip fractures

| | |
|----|-------------------------------------|
| A1 | Pertrochanteric simple |
| A2 | Pertrochanteric multi-fragmentary |
| A3 | Intertrochanteric |
| B1 | Subcapital with slight displacement |
| B2 | Transcervical |
| B3 | Subcapital, displaced, non-impacted |

forming units (CFU) of each of four probiotics: *Pedio-coccus pentoseceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* ssp 19, and *Lactobacillus plantarum* 2362. In addition, 2.5-g each of inulin, oat bran, pectin, and resistant starch was also given.

After hospital admission, patients were given the preparation; patients also had a Foley catheter until the second postoperative day. Administration of the preparation ceased 5 days after surgery or if vomiting and diarrhea started. All patients were stratified using the classification of the American Society of Anesthesiologists (ASA) (Table 1). Fractures were stratified using the Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification (Table 2).

Patients received 1.5 g of cefuroxime 30 min before surgery. Empiric treatment was initiated if an infection was present.

The infection was followed up by physical examination and laboratory analyses. Immediately after the patients had been hospitalized, we measured blood levels of C-reactive protein (CRP); we repeated this procedure on the fifth postoperative day. A clinical diagnosis of infection was made on the basis of: body temperature ($>38^{\circ}\text{C}$), rise in CRP level, clinical signs of infection, and positive culture. We looked at three main areas: (i) infection of the urinary tract (dysuria, leukocyturia, and positive uroculture); (ii) pneumonia (high body temperature, cough, auscultation, pulmonary infiltrates visible on chest radiographs); and (iii) wound infection (swelling, reddishness, positive bacterial culture). Subjective remarks from the patient (e.g., feeling of nausea) and objective signs (vomiting, diarrhea) were recorded.

Statistical analyses

All statistical analyses were made using SPSS for Windows (SPSS, Chicago, IL, USA). Qualitative data were compared using the two-tailed chi-square test. Quantitative data were expressed as medians plus ranges or means, with standard deviation of the mean. Differences between means were evaluated using analysis of variance (ANOVA) or paired the t-test, as appropriate. The Mann-Whitney U test was used to compare non-parametric data. $P \leq 0.05$ was considered significant. The statistical power of the study was 7%.

RESULTS

There were 26 patients in group A and 25 in group B. There were no significant differences between the groups with regard to: age; sex; CRP level on the day of hospital admission; the time between the day of injury and surgery; and the time of surgery. The two groups were also comparable with respect to pre-operative ASA score, the AO classification of fractures, and the surgical procedure (Table 3).

Table 4 summarizes the outcome in the two groups with respect to: infection; mortality; adverse events (objective and subjective appraisals); and differences in CRP level between day of hospital admission and postoperative day 5. Nine patients taking the placebo had self-reported difficulties, whereas 2 patients taking Synbiotic 2000 Forte had self-reported difficulties: this difference was statistically significant.

Table 5 shows the isolated infective agents. Infection was proved in 8 patients (4 in group A and 4 in the placebo group). Infection of the urinary tract was noted in 7 cases there was and a local wound infection was observed in 1 subject.

Table 3: Patient characteristics

| | Group A | Group B |
|--|-------------|-------------|
| Time between injury to surgery, days (SD) | 3.2 (2.8) | 2.8 (1.8) |
| Male:female | 7:19 | 7:18 |
| Mean age, years (SD) | 70 (12) | 73 (14) |
| Level of CRP on day of hospital admission (SD) | 11 (17) | 21 (32) |
| ASA preoperative score | | |
| ASA | | |
| 1 | 1 | 1 |
| 2 | 12 | 11 |
| 3 | 12 | 11 |
| 4 | 1 | 2 |
| AO classification of fracture | | |
| A1 | 1 | 4 |
| A2 | 9 | 11 |
| A3 | 7 | 5 |
| B1 | 2 | 0 |
| B2 | 6 | 2 |
| B3 | 1 | 3 |
| Surgical procedure | | |
| DHS | 5 | 4 |
| Hemiarthroplasty | 7 | 3 |
| PFNa | 12 | 16 |
| Cannulated screws | 2 | 2 |
| Duration of surgery in minutes, means (SD) | 53.1 (23.6) | 54.6 (25.8) |

Group A: Synbiotic 2000 Forte; group B: placebo

Table 6 shows the number of patients with infection according to the preoperative ASA classification. In patients with a higher ASA score (3 or 4) there were more cases of infection, but this difference was not statistically significant.

DISCUSSION

The present study showed that Synbiotic 2000 Forte did not reduce the prevalence of infections after surgical treatment of fractures in the proximal thigh

bone area. Synbiotic treatments have been shown to preserve (or even restore) immune functions, reduce inflammation, and bolster the body's resistance to disease (6). The efficacy of prebiotics and probiotics in preventing the onset of sepsis and multisystem organ dysfunction syndrome (MODS) has been examined in: multiple animal models; critically ill patients with severe pancreatitis; those undergoing abdominal surgery; liver-transplant patients (6, 9, 11, 12, 13). Kotzampassi et al. (12) treated patients with severe multiple trauma with Synbiotic 2000 Forte for 15 days.

Table 4: Clinical results: comparison between groups

| | Group A | Group B | P |
|--|-------------|-------------|------|
| Infection | 4 | 4 | 0.63 |
| Mortality | 1 | 1 | 0.75 |
| Problems with agent (subjective) | 2 | 9 | 0.02 |
| Problems with agent (objective) | 1 | 4 | 0.17 |
| Difference in CRP level between fifth postoperative day and hospital admission; means (SD) | 43,1 (34.4) | 46,1 (33.1) | 0.84 |

Group A: Synbiotic 2000 Forte; group B: placebo

Table 5: Site of infection and isolated microorganism

| Infection site | Isolated microorganism | Group |
|----------------|------------------------|-------|
| Urinary tract | Enterobacter spp. | A |
| Urinary tract | Pseudomonas aeruginosa | B |
| Urinary tract | Enterobacter spp. | B |
| Urinary tract | Pseudomonas aeruginosa | B |
| Urinary tract | Escherichia coli | B |
| Local wound | Enterococcus faecalis | A |
| Urinary tract | Escherichia coli | A |
| Urinary tract | Staphylococcus aureus | A |

Group A: Synbiotic 2000 Forte; group B: placebo

Table 6: Preoperative ASA score in number of infection by group

| | ASA | Total | |
|-----------|-----|-------------|-------------|
| | | 1, 2 (A, B) | 3, 4 (A, B) |
| Infection | No | 23 (12, 11) | 20 (9, 11) |
| | Yes | 2 (1, 1) | 6 (3, 3) |
| Total | | 25 (13, 12) | 26 (20, 6) |
| | | | 51 (25, 26) |

Group A: Synbiotic 2000 Forte; group B: placebo

Synbiotic-treated patients exhibited a significantly reduced prevalence of infection, sepsis, and mortality was noted in subjects treated with Synbiotic 2000 Forte.

Spindler-Vesel et al. (13) compared Synbiotic 2000 Forte with glutamine, fermentable fiber, and peptide diets in multiply injured patients. They found that pa-

tients given Synbiotic 2000 Forte developed fewer infections and showed significant improvements in gut barrier function.

Chermesh et al. (14) established the negative influence of synbiotics in Crohn's disease. They explained this finding as possibly being due to a small study cohort (30 subjects) and the drug regimen (synbiotics

given once a day). In the present study, we gave Synbiotic 2000 Forte immediately after hospital admission, and this agent was given twice a day.

In the present study, the overall prevalence of infection was to 15.7%, whereas that of urinary tract infection was 13.7% and that of local wound infection was 2%. Southwell-Kelly et al. (15) in their meta-analysis stated that the prophylactic use of antibiotics reduced the prevalence of local wound infection to 5% and that of urinary tract infection to 16%.

The results of the present study could have been influenced by the: heterogeneity of the groups; time interval between injury and surgery; patient's health before surgery. With respect to heterogeneity, the groups were not significantly different from each other.

Our patients underwent surgery at different times after hospital admission. This parameter was influenced by the (i) patient's health upon hospital admission and (ii) availability of the appropriate surgical team. Above all we wanted to treat the patient as soon as possible, which in practice meant a long time interval (0–16 days; usually 3 days after injury). Shiga et al. (16) demonstrated that the prevalence of complications increased in patients undergoing surgery >48 h after the injury. Orosz et al. (17) discussed the reasons for the postponement of operations and his results were in accordance with the present study. They noted that 24

patients (47%) underwent surgery <48 h after injury. In the present study, according to the prevalence of infections and mortality, the difference between the two groups was not significant.

We stratified patients according to the preoperative ASA classification (18). In patients with a higher ASA score (3 or 4), we noted a higher prevalence of infections than in patients with a lower ASA score.

The use of antibiotics for prophylactic purposes lowered, to a certain degree, the prevalence of infections after surgery of the hip joint. Nevertheless, this value was high and further studies are needed to find a new substance that can lower this prevalence.

The statistical power of the present study was low, primarily due to the small cohort. Perhaps the results would have been different with a larger cohort, particularly if patients underwent surgery <48 h after the injury. One must emphasize that this was a pilot study. Further studies must involve subjects matched by age, time interval between injury and surgery, AO classification, surgical procedure, and measurement of inflammatory mediators.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interests.

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