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THE EFFECT OF OMEPRAZOLE ON TREATMENT OUTCOMES IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY AND SEPSIS

WPŁYW OMEPRAZOLU NA WYNIK LECZENIA PACJENTÓW Z CIĘŻKIMI URAZOWYMI OBRAŻENIAMI MÓZGU I SEPSĄ

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Authors' contribution
Wkład autorów:
A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
G. Funds collection
zebranie funduszy

Summary

Background. The interrelation between omeprazole use and the possibility of developing nosocomial pneumonia, acute kidney damage and *Clostridium difficile*-induced diarrhea in patients with sepsis requires further study.
Material and methods. 200 patients with severe craniocerebral injury that underwent surgery for the pathology and developed sepsis in the postoperative period were examined in a blind, randomized placebo-controlled research study. The patients were divided into two groups. Patients in Group 1, as part of their therapy regimen for sepsis, received a daily dose of 0.2 mg/kg omeprazole as an intravenous infusion; patients in Group 2 received placebo instead of omeprazole, in addition to a similar therapy regimen as Group 1.
Results. Among patients receiving omeprazole, the number of concomitant ventilator-associated pneumonia cases increased by 1.32 times, the number of acute kidney damage cases by 1.33 times and the number of cases of *Clostridium difficile* toxin secretion with feces by 1.75 times.
Conclusions. The routine use of omeprazole in the management of patients with sepsis may worsen treatment results.

Keywords: omeprazole, ventilator-associated pneumonia, acute renal injury, sepsis, clostridial infection

Streszczenie

Wprowadzenie. Kwestia korelacji stosowania omeprazolu z możliwym rozwojem szpitalnego zapalenia płuc, ostrego uszkodzenia nerek czy biegunki wywołanej przez *Clostridium difficile* u pacjentów z sepsą wymaga dalszych badań.
Materiał i metody. W ślepym i randomizowanym badaniu kontrolowanym placebo przebadano 200 pacjentów z poważnymi obrażeniami czaszkowo-mózgowymi, którzy w wyniku tej patologii przeszli operację, i u których w okresie pooperacyjnym rozwinęła się sepsa. Zostali oni podzieleni na dwie grupy. Grupa 1 przyjmowała omeprazol w formie wlewu dożylnego w dziennej dawce 0,2 mg/kg jako część kompleksowego leczenia sepsy; grupa 2 przyjmowała placebo zamiast omeprazolu jako dodatek do głównej terapii, podobnej do tej stosowanej w przypadku grupy 1.
Wyniki. Wśród pacjentów przyjmujących omeprazol liczba przypadków towarzyszącego respiratorowego zapalenia płuc wzrosła o 1,32 raza, ostrego uszkodzenia nerek – o 1,33 raza, a wydalenia toksyn *Clostridium difficile* w kale – o 1,75 raza.
Wnioski. Rutynowe stosowanie omeprazolu w leczeniu pacjentów z sepsą może pogorszyć wyniki terapii.

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Słowa kluczowe: omeprazol, respiratorowe zapalenie płuc, ostre uszkodzenie nerek, sepsa, zakażenie *Clostridium*

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Introduction

Prevention and treatment of stress ulcers and gastrointestinal bleeding is one of the important tasks in the practice of anesthesiology. Sepsis, shock of differing etiologies, extensive trauma, craniocerebral trauma, multiple organ dysfunction syndrome, prolonged (more than 48 hours) artificial ventilation of the lungs and coagulopathy are risk factors for the development of stress-related erosive ulcers of the gastrointestinal tract (GIT), so-called "stress-related mucosal damage". The prevention of gastrointestinal bleeding in patients with sepsis who are on prolonged mechanical ventilation (MV) is particularly critical. The most recent Surviving Sepsis Guidelines, 2016 [1], recommend the routine use of proton pump inhibitors (PPI) in patients with long-term MV to prevent gastrointestinal bleeding. A growing number of studies on the effectiveness of PPIs and their side effects are published each year. Several randomized studies have shown that the use of PPIs can increase the risk of nosocomial pneumonia, acute kidney damage and *Clostridium difficile*-induced diarrhea in intensive care unit (ICU) patients [2,3]. Other randomized studies have confirmed the absence of similar pathologies on the background of PPI use in corresponding ICU patients [4,5]. Considering these discrepancies, the relationship between the use of PPIs and the possibility of developing nosocomial pneumonia, acute kidney damage and *Clostridium difficile*-induced diarrhea in patients with sepsis who are on prolonged MV requires further study.

Material and methods

The blind, randomized placebo-controlled research study included 200 patients with severe craniocerebral injury that underwent surgery for this pathology and subsequently developed sepsis in the postoperative period.

All patients were on prolonged MV. This study was part of the planned scientific research work of Ternopil National Medical University, Ukraine, "Development of new and improvement of existing methods and means of prevention, diagnosis and treatment of the most common and socially significant diseases" No. of state registration 0119U002307. The research was carried out in the Department of Anesthesiology and Intensive Care of Ternopil University Hospital during 2018 and 2019. Patients were included in the study as soon as they were diagnosed with sepsis. Diagnostic criteria for sepsis followed the Definition of Sepsis 2016 [1]. Additionally, the diagnosis was confirmed by a mandatory test of serum calcitonin levels. Sepsis was diagnosed if the procalcitonin level was above 2.0 ng/ml. Once the diagnosis of sepsis was established, patients were scored on the APACHE-II scale. This study included patients with craniocerebral trauma who had developed sepsis as a complication of the related surgery. Patients with pneumonia that occurred before the sepsis, which could be the cause of its development, were excluded from the study. In most cases, sepsis occurred 7-14 days after surgery. As all of the patients had severe disorders of consciousness and breathing, they were on MV.

Most of the patients were unconscious for a long period of time. For this reason, the informed consent to conduct the research was signed not by the patients but by the patients' close relatives who represented their legal interests. The planning materials and results were approved by the Bioethics Committee of Ternopil National Medical University.

Inclusion criteria:

- severe craniocerebral trauma,
- sepsis diagnosed according to the Definition of Sepsis 2016 [1], which was caused by surgical intervention for severe craniocerebral injury,
- the need for prolonged MV.

Exclusion criteria:

- pneumonia that occurred before sepsis was diagnosed,
- acute kidney damage that occurred before the sepsis was diagnosed,
- clostridial infection, which was diagnosed before the diagnosis of sepsis,
- use of nephrotoxic antibiotics,
- the presence of chronic kidney and lung diseases,
- gastric and duodenal ulcers,
- *Clostridium difficile*-induced intestinal infections before starting research.

Using a simple randomization method, patients were divided into two groups. Patients in Group 1, as part of their therapy regimen for sepsis, also received a daily dose of 0.2 mg/kg omeprazole by intravenous infusion; patients of Group 2 received a placebo instead of omeprazole in addition to the primary therapy, which was similar to that of Group 1. The patients were monitored for one month, all of them undergoing long-term MV. Patients received meropenem or second generation cephalosporins in combination with fluoroquinolones or aminoglycosides or piperacillin, or tigecycline or linezolid as antibiotic therapy. The duration of treatment for

a type of antibiotic therapy was on average 10-16 days, then, according to the antibioticogram, the antibiotics were changed. All patients received antibiotics in average doses during the entire period of observation, i.e., within a month. Due to the replacement of antibiotics, it was difficult to calculate the duration and frequency of each specific antibiotic administration. Considering the fact that we evaluated the nephrotoxicity of the therapy, it was important that nephrotoxic antibiotics, primarily aminoglycosides, were used. In Group 1, 18 patients received aminoglycosides, and, in Group 2, 20 patients received them. As soon as the possibility of postoperative bleeding was excluded, all patients received a low-molecular-weight heparin in a preventive dose. The frequency of ventilator-associated pneumonia (VAP), acute kidney damage symptoms and *Clostridium difficile*-induced diarrhea were compared in both groups. Pneumonia was diagnosed after chest X-ray examination. Kidney damage was determined based on creatinine and potassium levels in the blood. For statistical purposes, the highest creatinine index determined during the entire period of observation was recorded. To identify *Clostridium difficile*-induced diarrhea the "RIDASCREEN *Clostridium difficile* Toxin A/B" (R-Biopharm AG, Germany) test was performed to determine the content of A and B toxins in feces samples. The patients' conditions were assessed using the APACHE-II scale. APACHE-II scores were compared between groups. The highest value for this indicator during the observation period was recorded.

Statistical analysis included calculation of mean arithmetic values (M) and standard deviation (±SD). The data array was tested for normal distribution using the Shapiro-Wilk test. For the initial data with normal distribution, Student t-distribution was used to determine the statistical significance of different mean values. Statistical significance levels were calculated and considered significant at $p<0.001$. Microsoft Excel 2010 and StatSoft STATISTICA 10 software were used for calculations.

Results

The characteristics of the patients who took part in the research and statistical results of their clinical conditions are presented in Table 1. The average age of the patients in Group 1 was 48.6±5.6 years and in Group 2 was 46.3±3.8 years. Group 1 comprised 86 men (86%) and 14 women (14%); Group 2 comprised 82 men (82%) and 18 women (18%). The average duration of MV in Group 1 patients was 27.6±2.1 days and for Group 2 was 21.6±3.1 days. There was no significant difference between the two groups for APACHE-II scale evaluation scores.

Gram-negative flora prevailed in the postoperative wound secretions in most patients. For Group 1, microorganisms of the *Enterobacteriaceae* family were identified in 58 patients, *Klebsiella pneumoniae* in 5 patients, *Acinetobacter baumannii* in 9 patients and *Pseudomonas aeruginosa* in 1 patient. Also in Group 1, *Staphylococcus aureus* was identified in 15 patients and *Staphylococcus haemolyticus* in 12 patients. For Group 2, *Enterobactericae* microorganisms were identified in 56 patients, *Klebsiella pneumoniae* in 4 patients and *Acinetobacter baumannii* in 16 patients. In addition to the gram-negative microorganisms, *Staphyllococcus aureus* was identified in 12 patients and *Staphylococcus haemolyticus* in 12 for Group 2.

Table 1. Comparative clinical characteristics of patients with sepsis associated with severe craniocerebral trauma, depending on the use of omeprazole

Characteristics	Group 1 (n=100)	Group 2 (n=100)
Mean age of patients, years	48.6±7.6	46.3±6.8
Mean time of MV, days	27.6±3.1	21.5±2.1
Number of patients with VAP	29 (29%)	22 (22%)
Number of patients with symptoms of acute renal injury	36 (36%)	27 (27%)
Average blood serum creatinine level, mcmol/l	0.26±0.03	0.19±0.02*
APACHE II score	22.3±1.4	24.8±1.7
Number of patients with *Clostridium difficile* toxins in feces	7 (7%)	4 (4%)
Number of patients with gastrointestinal bleeding	4 (4%)	2 (2%)
Number of deceased patients	28 (28%)	22 (22%)

Notes: * indicates significant difference ($p<0.001$) compared with the similar index for Group 1.

The data in Table 1 indicates that the patients in the two groups were of similar ages. Patients in Group 1 were on MV 1.28 times longer ($p=0.05$). The amount of VAP in Group 1 was 1.32 times greater than in Group 2. Considering the question of primary cause—pneumonia leading to prolonged MV or prolonged MV causing pneumonia—we assumed that the primary problem was the occurrence of pneumonia.

In Group 1, the number of patients with symptoms of acute renal injury was 1.33 times the value in Group 2. This was accompanied by a 1.37 times increase in mean blood serum creatinine level in Group 1. The amount of fecal *Clostridium difficile* toxins in Group 1 was found to be 1.75 times the value in Group 2.

Group 2 clearly contained twice as many patients with acute gastrointestinal bleeding compared to Group 1, though the absolute values were relatively small—2 percent for Group 1 and 4 percent for Group 2. It should be noted that no bleeding case became lethal. Once bleeding occurred, the patients were withdrawn from the research and were administered conservative therapy, which proved effective in all cases.

Increased occurrence of VAP, acute renal injury and clostridial enterocolitis most likely resulted in the 1.27 times higher lethality observed in Group 1 compared with Group 2.

Discussion

The results from this study provide an opportunity to examine both the positive and negative effects of PPI use. PPIs are the most effective drugs for suppressing gastric acid secretion. They have been used in clinical practice for more than 25 years. In 2014, in Germany alone, 3.475 billion daily doses of PPI were administered [6]. However, this high level of use necessitates a critical analysis of the spectrum of their indications and the undesirable side effects that occur when they are administered. Medications of this group effectively inhibit basal and stimulated secretion of hydrochloric acid. This allows them to be considered drugs with high predictability of effect, providing more precise control of pH than H2-blockers. The ability of PPIs to reliably increase and maintain intragastric pH in ICU patients during MV and in the postoperative period at a level of at least 4 has been proven [6]. According to our research, the use of omeprazole, a medication with the properties of PPI, decreased the frequency of gastrointestinal bleeding in patients with severe sepsis from 4% to 2% in our patient groups. This result is clearly very positive, though the difference failed to reach statistical significance. It should also be noted that the occurrence of bleeding did not affect mortality rate.

Our data confirm the conclusions of a study by Blank et al. [7] indicating that the preventive prescription of medications increasing gastric secretion pH is accompanied by an increase in the potential risk of pneumonia. A meta-analysis of 96 relevant studies including 7,293 patients [5] showed that PPIs increase the risk of VAP development in the corresponding contingent of patients. Our data showed that VAP occurred 1.32 times more frequently in patients who received PPIs than in patients who received placebo. VAP is a highly dangerous manifestation of sepsis, which can increase the mortality of the corresponding contingent of patients up to 80%. The development of VAP is a prognostic sign of an unfavorable outcome in severe patients who require MV. VAP prolongs the duration of stay in the ICU, which, accordingly, leads to increased material costs for treatment of the disease and other complications [8]. We observed an increase in mortality rate among patients who received omeprazole and believe that it was primarily caused by an increase in VAP, which was observed in the same group. The effect of PPIs on inflammatory processes in pulmonary tissue is manifested by an increase in the number of pro-inflammatory factors, including molecules affecting adhesion in blood vessels, nitrogen oxide synthetase, tumor-necrotizing alpha factor and interleukins [9].

Another essential aspect of PPI application is the possible effect on development of *Clostridium difficile*-induced infections (CDI). Currently, the prevalence of such infections among ICU patients is estimated at 0.4-4% and has a serious impact on morbidity and mortality. CDI is a serious public health problem in terms of both disease outcome and economic impact [10]. For the patient, iatrogenic complication of treatment is painful and sometimes life-threatening. Without provision of treatment, lethality rate among patients with pseudomembranous colitis is 15–30%. According to our data, patients who received omeprazole were 1.75 times more likely to be diagnosed with *Clostridium difficile* toxins in their feces than patients who did not receive PPI. In our view, this fact may have a significant negative effect on treatment results, including an increase in mortality among the relevant contingent of patients. Thus, our data has confirmed findings by Buendgens et al. and Azab et al. that PPI increased the risk of spreading CDIs among patients in need of intensive therapy [11,12]. The mechanism by which PPI therapy contributes to the risk of CDI development is not clear. It has been suggested that the vegetative form of *Clostridium difficile* survives in a gastric pH above 4, the threshold for intestinal infections, including *Clostridium difficile* [13]. The risk of hospital-acquired CDI increases with increasing pH levels of gastric juice [14]. Hegarty and co-authors suggested that PPI therapy reduces the expression of genes that play an important role in the integrity of colonocytes, thereby contributing to the development of CDI [15]. Other studies have shown that prolonged use of PPIs reduces microbial diversity in the intestine [13].

According to a variety of data, acute renal injury occurs in 24-47% of ICU patients [16]. This pathology has a significant negative impact on the course and outcome of diseases requiring intensive care, especially sepsis. The increase in the number of cases of acute kidney damage and deterioration of kidney function in patients receiving omeprazole may have been an underlying reason for poorer results and outcomes with treatment.

Conclusions

The use of omeprazole for preventive purposes in routine treatment of sepsis after surgery for severe craniocerebral injury, despite a 2.0-fold decrease in the number of gastrointestinal bleedings, resulted in a 1.32-fold increase in concomitant VAP, a 1.33-fold increase in the number of cases of acute kidney damage and 1.75-fold increase in the number of cases of excretion of *Clostridium difficile* toxins with feces, which overall eventually led to a 6% increase in lethality rate in patients receiving omeprazole.

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