Biomedical Research 2018; 29 (3): 606-609 *ISSN 0970-938X*
www.biomedres.info

The influence of the use of metronidazole associated with vancomycin in reducing the mortality rate at 30 days in patients with *Clostridium difficile* infection.

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Abstract

Background: *Clostridium difficile* infection (CDI) still remains the most common cause of nosocomial diarrhea. We assumed that the death rate at 30 days could be influenced by the etiological therapy, monotherapy (vancomycin) alone versus the association of vancomycin with metronidazole. We considered as a secondary factor the association of chronic treatment with statins.
Methods: We assume that the administration of the actual etiological therapy at patients having CDI cannot be postulated as being similar for all molecules used alone or in combination, in all aspects, including the concerns regarding the mortality rates within 30 d, requiring concrete data related to this issue. We aimed to assess the mortality rate within 30 d in patients with CDI. We conducted an analytical, observational study. We have developed a logistic regression model to verify our hypothesis. The model is testing what are the factors increasing the odds of survival after treating the CDI at 30 d.
Results: The 525 enrolled patients were divided into two groups: statin non-users (n=454) and statin users (n=71). The antimicrobial exposure, the proton pump inhibitors exposure in last 60 d and the relapse rate were similar in both groups, but the death rate was lower in the group of patients that received as chronic treatment statins (1.4% versus 8.6%).
Conclusions: The addition of intravenous metronidazole to oral vancomycin for the treatment of CDI is associated with a significant reduction of the odds of death within 30 d.

Keywords: *Clostridium difficile* infections, Health care issue, Metronidazole, Vancomycin, Statins, Mortality rate.

Accepted on November 13, 2017

Introduction

Clostridium difficile infection (CDI) still remains the most common cause of nosocomial diarrhea, associating a relapse rate of 25-30% after the first episode, 40-60% after the second one, and also severe complications (toxic megacolon, colonic perforation, sepsis) and death [1-8].

In our effort to understand which are the main favorable factors behind the evolution of the *Clostridium difficile* infection, we assumed that the death rate at 30 days could be influenced by the etiological therapy of the CDI, monotherapy (vancomycin) alone versus the association of vancomycin with metronidazole. We considered as a secondary factor the association of chronic treatment with statins. Recent studies regarding the use of statins are contradictory in terms of the benefit in reducing the severity, complications or the mortality rate within 30 d [9-11]. Because no studies have been conducted on the study of the mortality rate at 30 d in patients receiving bi-therapy versus monotherapy, we paid attention primarily to this aspect.

Material and Methods

We assume that the administration of the actual etiological therapy at patients having *Clostridium difficile* infection cannot be postulated as being similar for all molecules used alone or in combination, in all aspects, including the concerns regarding the mortality rates within 30 d, requiring concrete data related to this issue. We aimed to assess the mortality rate within 30 d in patients with CDI, with moderate or severe clinical forms of the disease, patients that were under treatment with vancomycin or vancomycin associated with metronidazole.

We conducted an analytical, observational study. The analysis is performed using observational data collected from the electronic health records. The sample includes all patients having *Clostridium difficile* infection with moderate or severe clinical forms. Patients that were hospitalized during August 2013 to December 2015 in the Academic Emergency Hospital from Sibiu, Romania. A county hospital with 1054 beds, three intensive care unit services; general, vascular, thoracic surgery department, internal medicine, cardiology, neurology, hematology, oncology, and infectious diseases department. The diagnosis of CDI was carried out either by EIA (Enzyme Immunoassay), GDH (Glutamate Dehydrogenase) and/or colonoscopy. We excluded from the analysis all the cases that lacked complete data. The size of the sample used in the analysis is 525 cases. We included in the study demographic data like: age, gender, data regarding a pervious hospitalization for patients that underwent surgical procedures in last 2 months, Charlson Comorbidity score, previous antibiotic treatment, previous proton pump inhibitors exposure, CDI treatment, chronic treatment with statins, and the clinical outcome at 30 days. The patients evolution has been reported at the antibiotic treatment oral vancomycin alone or oral vancomycin in combination with intravenous metronidazole, and at the association with statins as a chronic treatment of these patients. Written informed consent was obtained from the patients on their admission to the hospital. The study was accepted by the Ethics Committee of the hospital and also by the University. The method employed for analyzing data is logistic regression. To this end, we have use IBM SPSS Statistics version 21.

We have developed a logistic regression model to verify our hypothesis. The model is testing what are the factors increasing the odds of survival after treating the CDI at 30 d.

Dependent variables

The dependent variable (death/survival of the patient) is measured as a dummy variable. The death of the patient is considered only within an interval of 30 d from the discharge of the patients.

Independent variables

We used as independent variables, the treatment of CDI that associates vancomycin and metronidazole (coded "1" if both vancomycin and metronidazole were administered, and "0" if only vancomycin was administered).

The severity of the patient's comorbidities was measured using Charlson Comorbidity score. In our analysis the Charlson Comorbidity score is recoded as a dummy variable (from 0 to 3 where coded as "0", and scores of 4 and above were coded "1").

Statins is also a dummy variable expressing if statins were administered to patients (coded "1" if they were administered and "0" if they were not administered).

We also included in the analysis the following control variables: the age of the patient (age was recoded so that the persons having 61+ y where coded "0" and persons between 18 and 60 y old where coded "1"), the number of days of hospitalization and the sex of the patient (where "1" denotes a male and "0" female).

Results

The 525 enrolled patients were divided into two groups: statin non-users (n=454) and statin users (n=71). In both groups of patients, most cases were recorded at female patients. The average age was higher in the statin users group 69.14 ± 7.97 y versus 64.2 ± 16.11 y for the statins non-users group. In both groups, patients showed similarities regarding the presence and the type of surgery that they underwent in the prior 2 months of the CDI episode except the cardiovascular surgeries (26.7% of statin users versus 6.2% of statin non-users). The patients from the statin group showed a higher percentage of myocardial infarction (56.3% versus 13.7%), congestive heart failure (78.8% versus 38.3%), stroke disorders (29.5% versus 7.9%), cerebrovascular disorders (52.1% versus 35.2%), chronic venous insufficiency (46.4% versus 21.4%), and a Charlson Comorbidity score ≥ 4 at 70.4% versus 40.1% of patients. The antimicrobial exposure, the proton pump inhibitors exposure in last 60 days and the relapse rate were similar in both groups, but the death rate was lower in the group of patients that received as chronic treatment statins (1.4% versus 8.6%). From the 525 enrolled patients, we recorded 40 deaths at 30 d.

The characteristics of the patients at the time of the enrolment are presented in Table 1.

Table 1. *Baseline characteristics of the patients.*

Characteristics	Statin non-users (n=454)	Statin users (n=71)
Age (mean, Std. deviation, min., max.) years	64.2 ± 16.11; 18; 94;	69.14 ± 7.97; 53; 85;
Sex (female)	255 (56.2%)	39 (54.9%)
Patients that underwent surgical management in last 2 months:		
-Abdominal surgery	96 (21.1%)	17 (23.9%)
-Malignant tumor	40 (8.8%)	3 (4.2%)
-Cholecystectomies	36 (7.9%)	13 (18.3%)
-Urology	33 (7.3%)	4 (5.6%)
-Orthopedics/traumatology	23 (5.1%)	0
-Neurosurgery	10 (2.2%)	0
-Cardiovascular	28 (6.2%)	19 (26.7%)
-Gynecology	10 (2.2%)	1 (1.4%)
Charlson comorbidity score		
≤ 3	272 (59.9%)	21 (29.5%)
≥ 4	182 (40.1%)	50 (70.4%)

Comorbidities:		
-COPD*	64 (14.1%)	14 (19.7%)
-Myocardial infarction	62 (13.7%)	40 (56.3)
-Congestive heart failure	174 (38.3%)	56 (78.8%)
-Diabetes	76 (16.7%)	17 (23.9%)
-Chronic renal failure	61 (13.4%)	11 (15.4%)
-Solid tumors	75 (17.5%)	8 (11.2%)
-Malignant hemopathies	33 (7.3%)	2 (2.8%)
-Cirrhosis	82 (18.1%)	14 (19.7%)
-Post stroke disorders	36 (7.9%)	21 (29.5%)
-Dementia	67 (14.8%)	14 (19.7%)
-Cerebrovascular disorders	160 (35.2%)	37 (52.1%)
-Chronic venous insufficiency	97 (21.4%)	33 (46.4%)
-Duodenal ulcer	132 (29.1%)	21 (29.5%)
Antimicrobial exposure in last 60 d	359 (79.1%)	56 (78.8%)
Proton pump inhibitors exposure in last 60 d	273 (60.13%)	46 (64.7%)
Patient outcome		
1st relapse	91 (20.04%)	17 (23.9%)
2nd relapse	29 (6.39%)	4 (5.6%)
3rd/more than 3 relapses	8 (1.76%)	2 (2.8%)
Deaths	39 (8.6%)	1 (1.4%)
*COPD: Chronic Obstructive Pulmonary Disease		

The results of the statistical analysis through logistic regression are presented in Table 2.

Table 2. *Logistic regression, dependent variable: decease of the patient (N=525).*

Independent variables	**Death of the patient (at 30 d)**		
	B	**Wald**	**Exp (B)**
Constant	-2.327***		
Age (18 to 60=1)	-0.637	2.069	0.529
Sex (1=male)	0.328	0.92	1.389
Number of days of hospitalization	0.015	0.293	1.015
Statins (1=yes)	–2.106*	4.153	0.122
V+M* (1=yes)	–1.124***	10.647	0.325
Charlson score (1=4+)	0.826*	5.458	2.284
Dependent variables			
Cox and Snell R Square	0.05		
Nagelkerke R Square	0.12		
Omnibus test (model)	χ^2=26.921; df=6; p=0.000		
Hosmer and Lemeshow Test	χ^2=14.078; df=8; p=0.080		
-2Log likelihood	255.913		

Note: ***p<0.001, **p<0.01, *p<0.05, +p<0.1; V+M: Vancomycin+Metronidazole.

The relation of the dependent variable with the set of predictors is supported by the results of the analysis. However, considering the sample is not probabilistic, not representative, the results should be read with caution. An accurate reading of the significance levels in both models is: if the sample were representative, then the results obtained could be extended for the whole population of persons having *Clostridium difficile* infection with a probability of "p."

The results presented in Table 2 indicate that the main variable in terms of its predictive value turns out to be vancomycin plus metronidazole. It is followed by statins and the Charlson Comorbidity score.

Discussions

Studies in the literature concerning the association of intravenous metronidazole treatment with oral vancomycin for the treatment of the first, mild or moderate episode of CDI, did not indicate the reductions of the rate of recurrences. Moreover, the use of metronidazole alone, for the treatment of the first episode of CDI, it led to an increasing of the failure treatment in Canada, from 9.6% in the years of 1991-2002 to 26% in 2004 [12] or even an increased mortality as published in the study by Musher et al. [13]. Other studies also suggested that clinical improvement under treatment with metronidazole was slowly compared to vancomycin [14], and that might be correlated with the increasing of the minimum inhibitory concentration [15]. The association of intravenous metronidazole with oral or per rectum vancomycin, according to the Clinical practice guidelines for *Clostridium difficile* infection in adults, is addresses only to severe or complicated forms of CDI [4]. In our study, the recurrence rate was not inferior to the rate from the treatment only with vancomycin but was correlated with a reduced rate of death within 30 d.

The addition of intravenous metronidazole to oral vancomycin has a negative significant relation with the dependent variable, the odds of death within a 30 d period are about 67% smaller for the patient taking both antibiotics than for the patients being treated with oral vancomycin, holding all the other predictor constant. A similar relation with the dependent variable is found in respect statins; that is, the odds of death within a 30 d period are about 87% smaller for the patient taking statins than for the other patients, holding all the other predictor constant. The positive relation of the Charlson Comorbidity score with the dependent shows that the patients having severe illness are about 2,83 more likely to die within a 30 d period than those who have a maximum Charlson Comorbidity score of 3.

Conclusions

The addition of intravenous metronidazole to oral vancomycin for the treatment of *Clostridium difficile* infection is associated with a significant reduction of the odds of death within 30 d. Although there are no significant changes in the rate of relapse, the association of intravenous metronidazole to oral vancomycin would be considered in the next studies, together with statins, being a possible interrelation of the anti-inflammatory effects of the two molecules: metronidazole and statins.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patients on their admission to the hospital when their consent was requested for all their laboratory investigations that would be performed. The study was accepted by the Ethics Committee of the hospital and also by the University. No other additional consent was required for the study as this is an observational one.

Funding

Financial support was received for publishing the article through an internal competition for individual research grants within Lucian Blaga University of Sibiu, Romania, grant number 2032/8/25.05.2015.

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