

Pre-Stroke Use of Beta-Blockers Does Not Lower Post-Stroke Infection Rate: An Exploratory Analysis of the Preventive Antibiotics in Stroke Study

Willeke F. Westendorp^a Jan-Dirk Vermeij^a Matthijs C. Brouwer^{a, b}
Y.B.W.E.M. Roos^a Paul J. Nederkoorn^a Diederik van de Beek^{a, b} for the PASS
Investigators

^aDepartment of Neurology, Academic Medical Center, and ^bCentre of Infection and Immunity Amsterdam, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Key Words

Cerebrovascular disease/stroke · Infection · Pneumonia · Immune suppression · Beta-blocker

Abstract

Background: Stroke-associated infections occur frequently and are associated with unfavorable outcome. Previous cohort studies suggest a protective effect of beta-blockers (BBs) against infections. A sympathetic drive may increase immune suppression and infections. **Aim:** This study is aimed at investigating the association between BB treatment at baseline and post-stroke infection in the Preventive Antibiotics in Stroke Study (PASS), a prospective clinical trial. **Methods:** We performed an exploratory analysis in PASS, 2,538 patients with acute phase of stroke (24 h after onset) were randomized to ceftriaxone (intravenous, 2 g per day for 4 days) in addition to stroke unit care, or standard stroke unit care without preventive antibiotic treatment. All clinical data, including use of BBs, was prospectively collected. Infection was diagnosed by the treating physician, and independently by an expert panel blinded for all other data. Multivariable analysis was performed to investigate the relation between BB treatment and infection rate. **Results:** Infection, as defined by the physician, occurred in 348 of 2,538 patients

(14%). Multivariable analysis showed that the use of BBs at baseline was associated with the development of infection during clinical course (adjusted OR (aOR) 1.61, 95% CI 1.19–2.18; $p < 0.01$). BB use at baseline was also associated with the development of pneumonia (aOR 1.56, 95% CI 1.05–2.30; $p = 0.03$). Baseline BB use was not associated with mortality (aOR 1.14, 95% CI 0.84–1.53; $p = 0.41$) or unfavorable outcome at 3 months (aOR 1.10, 95% CI 0.89–1.35; $p = 0.39$). **Conclusions:** Patients treated with BBs prior to stroke have a higher rate of infection and pneumonia.

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Introduction

Infections frequently complicate the acute phase of stroke and have been associated with unfavorable outcome in stroke patients [1]. The high risk for post-stroke infection is at least partly driven by a stroke-induced immune suppression, which is hypothesized to be caused by increased sympathetic activity [2]. In an experimental study, administration of beta-blockers (BBs) after the onset of stroke was found to decrease the risk of infection [3]. It has been suggested that in stroke patients, administration of BBs in the acute phase after stroke could influ-

ence the immune suppression associated with acute stroke and decrease the risk of infections after stroke. Two recent cohort studies reported conflicting results on the association between BBs use and occurrence of infections in patients with acute stroke [4, 5].

This study is aimed at analyzing whether BB treatment influenced post-stroke infection in patients included in the Preventive Antibiotics in Stroke Study (PASS), a randomized open-label masked endpoint clinical trial on the efficacy and safety of preventive ceftriaxone in adults with acute stroke [6].

Methods

We investigated whether infection risk differs between patients treated with BB prior to stroke and BB naive patients. Therefore, all patients included in the intention-to-treat population of PASS were included in the current study. In PASS, adult patients in the acute phase of ischemic or hemorrhagic stroke (within 24 h after onset) with a National Institutes of Health Stroke Scale (NIHSS) score of 1 or higher, were randomized to receive ceftriaxone (intravenous, 2 g per day for 4 days) in addition to stroke unit care, or standard stroke unit care without preventive antibiotic treatment. We excluded patients with an infection at admission, using antibiotics within 24 h of randomization, with a known allergy to antibiotics, and patients in whom death was imminent. The trial protocol, statistical analysis plan, and main article of the study results have been published before [6]. Since the current analysis was not pre-planned in the PASS statistical analysis plan, it should be regarded as an exploratory analysis.

Baseline characteristics, clinical parameters, and endpoints were prospectively collected in case record forms that were filled out by the treating physician. Pneumonia, urinary tract infection (UTI), and other infections in the PASS were diagnosed by the treating physician and scored by an expert panel of 2 independent experts who were blinded for treatment allocation and adhered to the Centers for Disease Control and Prevention criteria [7]. Pre-stroke use of BBs was prospectively recorded at baseline for all patients based on the observational studies and hypotheses mentioned in the introduction. In the Netherlands, it is standard care to continue antihypertensive medication used at home during hospital admission for acute stroke.

Differences in baseline characteristics of patients with or without BB therapy prior to stroke are shown as percentages or mean (with SD) or median values (with interquartile range). We tested whether baseline characteristics were associated with infection overall and pneumonia and UTI separately by t test, Mann-Whitney U or chi-square test when appropriate. Included baseline characteristics were: age, sex, ethnicity, medical history prior to stroke (atrial fibrillation/flutter, stroke, myocardial infarction, cardiac valve disease, peripheral vascular disease, hypertension, hypercholesterolemia, pulmonary obstructive disease, diabetes mellitus, alcoholism, malignancy), medication used prior to stroke (anticoagulants, antiplatelet therapy, statins, ACE-inhibitors, BBs, proton pump inhibitors), smoking status, disability prior to stroke, phys-

ical examination at admission (heart rate, systolic/diastolic RR, temperature), stroke severity (NIHSS), dysphagia, use of urinary catheter, stroke type, acute treatment (intravenous or intra-arterial thrombolysis, coagulant therapy), and randomization. Characteristics with an association in univariate analysis ($p < 0.05$) were included in multivariate analysis. Variables known to have a strong association with infection were a priori included in multivariate analysis; these were: age, stroke severity, presence of dysphagia, and urinary catheterization. Association of BBs therapy and mortality at discharge and 3 months, and unfavorable functional outcome on the modified Rankin Scale (mRS 3–6) was estimated in univariate analysis and subsequent regression analysis including strong prognostic baseline variables, as described in the PASS protocol (age, stroke severity, history of stroke or diabetes, prior disability on mRS at admission). Because immune suppression is most pronounced and infection rate higher in the first days after stroke, we performed a subgroup analysis on infections within the first week. All analyses were performed with IBM SPSS statistics version 22.

Results

From July 6, 2010 to March 23, 2014, 2,538 patients were included in PASS: 84% of patients had ischemic stroke, 11% hemorrhagic stroke, 4% transient ischemic attack, and 2% had another diagnosis. At baseline, 885 of 2,538 patients (35%) used BBs. Baseline characteristics of these patients are shown in table 1. Patients using BBs prior to stroke were older; more often had a history of atrial fibrillation, stroke, hypercholesterolemia, hypertension, myocardial infarction, cardiac valve disease, and peripheral vascular disease and used more medication prior to stroke. Disability prior to stroke and stroke severity were similar between patients who used BBs and those who did not.

Infection, as defined by the physician, occurred in 348 patients, 130 (10%) in the ceftriaxone group and 218 (17%) in the control group. In one of these patients, baseline use of BBs was unknown; this patient was excluded from analysis. Infection was diagnosed within the first week in 270 patients by the physician and in 98 patients according to expert panel [6].

Infection rates were higher in patients using BBs at baseline, as compared to patients not using BBs (table 2). Adjusted OR (aOR) for the use of BBs at baseline and post-stroke infection was 1.61 (95% CI 1.19–2.18; $p < 0.01$; table 3); for the expert panel definition for infection aOR was 1.64 (95% CI 1.08–2.50; $p = 0.02$). Additional analyses restricted to infection occurring in the first week after stroke showed similar results (data not shown).

BB use at baseline was associated with stroke-associated pneumonia, as defined by physician (crude OR

Table 1. Baseline characteristics of patients treated with BBs pre-stroke vs. patients not treated with BB before stroke

	BB before stroke (n = 885)	No BB before stroke (n = 1,648)
Age, years, median (interquartile range)	77 (69–83)	71 (60–80)
Gender, male, n (%)	476/885 (5)	965/1,648 (6)
History, n (%)		
Atrial fibrillation/flutter	248/884 (28)	143/1,648 (9)
Stroke	357/884 (40)	468/1,648 (28)
Hypercholesterolemia	320/875 (37)	343/1,640 (21)
Hypertension	695/881 (79)	700/1,648 (42)
Myocardial infarction	207/884 (23)	123/1,648 (7)
Cardiac valve disease	104/885 (12)	68/1,646 (4)
Peripheral vascular disease	95/883 (11)	93/1,642 (6)
Obstructive pulmonary disease	79/885 (9)	129/1,644 (8)
Immunocompromise	25/885 (3)	59/1,648 (4)
Current smoker, n (%)	157/871 (18)	462/1,634 (28)
Prior medication, n (%)		
Anticoagulants	177/885 (20)	105/1,647 (6)
Antiplatelet	491/885 (55)	524/1,647 (32)
Statin	480/884 (54)	464/1,647 (28)
ACE-inhibitor	339/882 (38)	304/1,648 (18)
Proton pump inhibitor	347/883 (39)	308/1,647 (19)
mRS score	0 (0–1)	0 (0–1)
NIHSS	5 (3–10)	5 (3–9)
Dysphagia, n (%)	237/832 (28)	384/1,534 (25)
Bladder catheter, n (%)	176/881 (20)	277/1,645 (17)
Thrombolysis, n (%)	284/885 (32)	550/1,648 (33)
Randomization to ceftriaxone, n (%)	428/885 (48)	838/1,648 (51)
Stroke type (hemorrhagic stroke vs. other), n (%)	76/885 (9)	192/1,648 (12)

Table 2. Infection rate and outcome in patients using BB before stroke vs. patients not using BB before stroke

	BB before stroke (n = 885)	No BB before stroke (n = 1,648)	OR (95% CI)
<i>Physician diagnosis, n (%)</i>			
Infection	168/885 (19)	179/1,648 (11)	1.92 (1.53–2.42)
Pneumonia	79/885 (9)	80/1,648 (5)	1.92 (1.39–2.65)
UTI	79/885 (9)	93/1,848 (5)	1.64 (1.20–2.24)
Other infection	23/885 (3)	27/1,648 (2)	1.60 (0.91–2.81)
<i>Expert panel diagnosis, n (%)</i>			
Infection	62/885 (7)	67/1,648 (4)	1.78 (1.25–2.54)
Pneumonia	30/885 (3)	27/1,648 (2)	2.11 (1.24–3.57)
UTI	33/885 (4)	43/1,648 (3)	1.45 (0.91–2.29)
Other infection	4/885 (0.5)	5/1,648 (0.3)	1.49 (0.40–5.57)
<i>Outcome, n (%)</i>			
Mortality at discharge	85/884 (9.6)	60/1,647 (3.6)	1.85 (1.28–2.70)
Mortality at 3 months	123/880 (14.0)	144/1,639 (8.8)	1.67 (1.30–2.17)
Unfavorable outcome at 3 months	392/880 (45)	592/1,629 (36)	1.41 (1.19–1.66)

Table 3. Risk factors for infection (physician diagnosis)

Characteristic	Infection (n = 348)	No infection (n = 2,190)	Multivariate analysis aOR (95% CI)	p value
Age, years, median (interquartile range)	79.5 (72–86)	72 (62–80)	1.04 (1.02–1.05)	<0.01
Gender, male, % (n)	46 (160/348)	59 (1,284/2,190)		
History, % (n)				
Atrial fibrillation/flutter	23 (81/348)	14 (310/2,190)		
Stroke	34 (119/348)	32 (708/2,190)		
Hypercholesterolemia	22 (78/348)	27 (587/2,190)		
Hypertension	63 (219/348)	54 (1,181/2,190)		
Myocardial infarction	15 (53/348)	13 (278/2,190)		
Cardiac valve disease	7 (24/348)	7 (149/2,190)		
Peripheral vascular disease	11 (37/348)	7 (153/2,190)	1.76 (1.09–2.84)	0.02
Obstructive pulmonary disease	11 (38/348)	8 (170/2,190)		
Diabetes mellitus	23 (81/348)	19 (421/2,190)		
Alcoholism	4 (14/348)	5 (107/2,190)		
Malignancy	11 (38/348)	9 (196/2,190)		
Immunocompromise	3 (12/348)	3 (72/2,190)		
Current smoker, % (n)	15 (51/348)	26 (569/2,190)		
Prior medication, % (n)				
Anticoagulants	15 (52/348)	11 (231/2,190)		
Antiplatelet therapy	44 (153/348)	39 (865/2,190)		
Statins	39 (134/348)	37 (815/2,190)		
ACE-inhibitors	29 (100/348)	25 (544/2,190)		
BBs	48 (168/348)	33 (717/2,190)	1.61 (1.19–2.18)	0.01
Proton pump inhibitors	27 (95/348)	26 (560/2,190)		
mRS	0 (0–2)	0 (0–1)		
NIHSS	11 (6–16)	4 (3–8)	1.09 (1.06–1.12)	<0.01
Dysphagia, % (n)	60 (186/310)	21 (437/2,061)	2.90 (2.10–4.01)	<0.01
Bladder catheter, % (n)	52 (181/347)	12 (272/2,184)	3.95 (2.91–5.36)	<0.01
Stroke type (bleeding vs. other), % (n)	17 (60/348)	10 (209/2,190)	1.79 (1.14–2.82)	0.01
Randomization to ceftriaxone, % (n)	37 (130/348)	52 (1,138/2,190)	0.53 (0.40–0.70)	<0.01

1.92, 95% CI 1.39–2.65; $p < 0.001$). Advanced age, ethnicity, history of atrial fibrillation/flutter, obstructive pulmonary disease, malignancy, current smoking status, diastolic and systolic blood pressure, score on NIHSS, disability prior to symptoms (mRS), dysphagia, coagulant therapy, and stroke type were also associated with stroke-associated pneumonia in univariate analysis. After correction for these factors in a multivariable analysis, the aOR for BBs and pneumonia was 1.56 (95% CI 1.05–2.30; $p = 0.03$). Analyses using the expert panel definition for pneumonia showed a similar trend for BBs use and increased risk of stroke-associated pneumonia (aOR 1.76, 95% CI 0.92–3.36; $p = 0.09$).

The crude OR for BBs and diagnosis of UTI as defined by the physician was 1.64 (95% CI 1.20–2.34; $p < 0.01$). Advanced age, male sex, atrial fibrillation/flutter, hypertension and hypercholesterolemia, current smoking sta-

tus, stroke severity, presence of bladder catheter, treatment with thrombolysis, stroke type, and randomization were included in the multivariate analysis, showing an aOR for BBs and UTI of 1.25 (95% CI 0.85–1.83; $p = 0.25$).

Baseline BB use was associated with an unfavorable outcome (table 3), but these associations did not remain significant after correction for other prognostic variables as mentioned in the methods section (aOR for mortality at 3 months 1.14, 95% CI 0.84–1.53; $p = 0.41$; aOR for unfavorable outcome at 3 months 1.10, 95% CI 0.89–1.35; $p = 0.39$).

Discussion

In our analysis, BBs were not protective for post-stroke infection. In contrast to previous studies, we found that baseline use of BBs was associated with a

higher risk for infection. The previous 4 studies on BB treatment and infection risk reported that BBs were either associated with decreased infection risk or there was no association [4, 5, 8, 9]. All studies had a retrospective study design and were heterogeneous with respect to stroke type (ischemic or hemorrhagic) and definitions of BB use (prior to stroke or after stroke admission) and infections. In the previous 4 studies, definition of infection was not described in 2 studies. It was based on adverse event recording in one study, and in the other study modified CDC criteria were used. Our study had a prospective study design and predefined definition of infection, according to international consensus [10]. Data on BB treatment was prospectively collected and our large sample gave us the statistical power to perform multivariable analysis.

Baseline use of BBs was associated with a higher risk for infection. However, patients on BBs were older, more often had comorbidities, and used more medication than patients not on BBs. It has been well-recognized that patients with advanced age are more vulnerable for infections than previously healthy patients. Also, some comorbidities and medications are associated with infection [11, 12]. By performing multivariate analysis, we tried to correct this higher baseline infection risk in BB-treated patients, but it is possible that confounding by indication might have influenced the results. Also, mortality rate was higher in patients treated with BBs. This introduces a competing risk bias: deceased patients are not at risk of infection.

The etiology of stroke-associated infection is multifactorial. Infection occurs more often in patients with more severe stroke and advanced age; dysphagic patients are at a high risk for pneumonia, and patients with indwelling catheter for UTI. Also, post-stroke immune suppression, which could be mediated by hypothalamo-pituitary-adrenal axis and sympathetic nervous system activation, increases the infection risk [2, 3, 12]. Stroke-associated respiratory syndrome includes pneumonia, but also respiratory tract infections without chest-X-ray abnormalities and even a subset of these syndromes could be inflammatory rather than infective [13]. In a recent consensus of the 'Pneumonia in Stroke Consensus Group', it was agreed that the spectrum of lower-respiratory-tract-infections in the first 7 days after acute stroke are named as stroke-associated-pneumonia. In this study, these criteria for diagnosis were used. From previous experimental and clinical studies, it is thought that adrenergic effects on peripheral blood immune cells could enhance immune suppression and increase the infection risk, and BBs have the

potential to diminish these effects [14]. The results of this study do not support such an effect for pre-stroke use of BBs. Yet, effects of BBs have been shown to be dose dependent, and dosage dependent effects could have been missed since the dosage of BB therapy was not controlled in this study [15]. Also, effects might differ between BBs already used prior to stroke, as compared to BBs started directly after stroke [5]. Only a randomized clinical trial could investigate the true potential of BB treatment for reducing stroke-associated infections, but the results of this study are not encouraging.

This study has several limitations. First, only pre-stroke BB use was investigated. In previous studies, stronger associations were found for on-stroke treatment with BB. Second, use of BBs was strictly defined, but the class of drug, dose, and compliance of BB use at baseline was not. This treatment was recorded by the physician in a prospective manner, but the treatment itself, including dosage, was not recorded. In the Netherlands, it is a standard practice to continue antihypertensive medication used prior to stroke during hospital stay after stroke, and in the PASS no standard protocol was used for discontinuation of antihypertensive treatment during admission. Any discontinuation of treatment after randomization could theoretically have led to an underestimation of the effect of BBs, and dosage dependent effects could have been missed. Also, we did not distinguish between selective and non-selective BBs. These different classes could have differing working mechanisms; however, for both groups associations with immune response and infection have been described [4]. Third, this study is a cohort study, which contains the risk of selection bias. The population of the PASS had relatively mild stroke and a low rate of infection. This could theoretically have diminished the potential of the effect of BB therapy, but, since the infection rate was unchanged or even higher in BB treated patients, such an effect is unlikely. Finally, we were able to perform multivariable analysis because of the large study population, however because diagnosis of pneumonia by expert panel was made in a limited number of patients, this multivariable analysis contained more variables than statistically appropriate and should therefore be interpreted with caution.

Conclusion

Patients treated with BBs prior to stroke have a higher rate of infection and pneumonia, but not of UTI.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

Authors Contributions

W.F.W. wrote this manuscript together with D.B. and J.-D.V., M.C.B., Y.B.W.E.M.R. and P.J.N. commented on the paper. All authors agreed to the final version. All authors were involved in the design of the PASS and collection of data.

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