Prevalence and Associated Clinical Factors of GERD (Gastro-Esophageal Reflux Disease) in Ischemic Stroke Patients

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Abstract

Purpose: Aspirin is protective against ischemic stroke, but its use is a significant risk factor for gastro-esophageal reflux disease (GERD). We investigated the prevalence and associated clinical factors of GERD in ischemic stroke patients treated with aspirin.

Methods: We recruited 116 ischemic stroke outpatients who were receiving aspirin. Sixteen patients who had received proton pump inhibitors or H2 receptor antagonists within the previous month were excluded. The presence of GERD was defined using the GerdQ questionnaire, with a score of 8 or higher considered positive for GERD. Logistic regression analysis was conducted using variables which exhibited a significant correlation coefficient on two-group comparison as factors, with the presence or absence of GERD as the dependent variable.

Results: Mean age of the 100 patients analyzed was 69.3 ± 8.9 years. The prevalence of GERD was 28%. Mean BW of patients with GERD was significantly higher than of those without GERD (P =0.02). The proportion of patients receiving angiotensin II receptor blockers (ARBs) was significantly lower in the GERD group (P=0.04). In contrast, no significant difference was seen in the proportion of patients receiving calcium channel blockers (CCBs). Multivariable logistic regression analysis showed that ARB disuse and increased BW were independent predictors of GERD.

Conclusions: The prevalence of GERD was 28% in ischemic stroke patients treated with aspirin. Increased BW as well as ARBs disuse was independent risk factors of GERD. With all these factors, ARBs appear to be better suited than CCBs for use in patients with ischemic stroke with regard to the prevention of GERD. A comprehensive understanding of the relationship between ARBs and GERD prevalence awaits additional studies in a larger number of patients.

Keywords: GERD; Ischemic stroke; GerdQ; ARB; Protection

Introduction

Gastro-esophageal reflux disease (GERD) is defined as the condition that develops when the reflux of stomach contents causes troublesome symptoms or complications, including reflux esophagitis (RE) [1], and is common in daily clinical practice [2]. Although aspirin is frequently used as an antiplatelet agent in patients with ischemic stroke [3], owing to its ability to reduce overall stroke rates in secondary stroke prevention [4], it has recently been considered a risk factor for GERD symptoms [5,6].

The association between aspirin and GERD is well established, but few studies have examined the relationship between oral aspirin and GERD in ischemic stroke patients.

Here, we investigated the prevalence and associated clinical factors of GERD in patients with ischemic stroke patients treated with aspirin.

Methods

The subjects were ischemic stroke patients who had been treated in the outpatient clinic of the Ryotenkai Katagi Neurosurgery in April and May 2012. Enrollment was limited to ischemic stroke patients aged > 20 years from whom written informed consent was obtained. All study patients underwent antithrombotic low-dose aspirin therapy (81-100mg /day) and gastric coating agents. Patients who had received proton pump inhibitors or H2 receptor antagonists within 1 month or who had life-threatening complications were excluded. Patients were met prior to GerdQ questionnaire by the researcher to discuss the study, obtain informed consent from patients willing to take part, and

scheduled an interview. The study was conducted in accordance with the principles of the Declaration of Helsinki.

GerdQ questionnaire

GerdQ is a well-documented questionnaire which was developed under a rigorous evidence-based approach [7,8]. In one study, patients with a GerdQ score of 8 or higher were regarded as having GERD, and a clinical approach based on this classification was shown to provide lower health care costs than an empirical approach without any loss of efficacy [9]. Following these findings, GerdQ is now considered a useful tool for the diagnosis of GERD without the need for specialist referral or endoscopy (gastroenterological evaluation).

Study design

After obtaining written informed consent, we enquired about GERD symptoms using the GerdQ questionnaire (Table 1). In brief, GerdQ scores the frequency of six items: 1) heartburn, 2) regurgitation,

Question	Frequency score (points) for symptom			
	0 day	1 day	2-3 days	4-7 days
1. How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3
3. How often did you have pain in the centre of the upper stomach?	3	2	1	0
4. How often did you have nausea?	3	2	1	0
5. How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3
6. How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take?	0	1	2	3

Table 1: GerdQ questionnaire.

3) dyspepsia, 4) nausea, 5) sleep disturbance, and 6) need for over-the-counter (OTC) treatment during the past 7 days using a 4-point scale with a score range of 0 to 3 (0=0 days/week; 1=1 day/week; 2=2-3 days/week; and 3=4-7 days/week). In accordance with previous reports, patients with a GerdQ score of 8 or higher of a maximum possible score of 18 were regarded as having GERD (7-9). Endoscopy was not performed. Medical records and drug history were retrospectively surveyed to clarify factors involved in GERD.

Survey items

Age, gender, height, body weight (BW), type of stroke (atherothrombotic, lacunar, cardioembolic, and transient ischemic attack), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (PR) were recorded. The presence or absence of hypertension (use of antihypertensive agents, systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg before stroke onset); dyslipidemia (use of lipid-lowering agents; or serum levels of TC >220 mg/dL, TG >150 mg/dL, LDL-C >140 mg/dL and/or HDL-C <40 mg/dL); type 2 diabetes mellitus (use of oral hypoglycemic agents or insulin, fasting blood glucose >126 mg/dL, or glycosylated hemoglobin level >6.5%); and smoking habit (smoking during the preceding 12 months) was determined.

Information on concomitant medication including antihypertensive agents (angiotensin II receptor blockers, ARBs; calcium channel blockers, CCBs; diuretics; angiotensin-converting enzyme inhibitors, ACEIs; beta blockers and alpha blockers), lipid-lowering agents (hydroxymethylglutaryl coenzyme A reductase inhibitors, statins; ezetimibe; eicosapentaenoic acid, EPA), glucose-lowering agents (sulfonylurea; dipeptidyl peptidase 4 inhibitors, DPP4 inhibitors; thiazolidinedione derivatives, TDs; andα-glucosidase inhibitors, α-GIs) and insulin was collected.

Statistical analysis

Continuous values were expressed as the mean ± SD. Subjects were divided into two groups using a GerdQ score of 8 points as cut-off. The significance of differences in mean values and proportions was tested using Student's t-test for continuous variables and the chi-squared test for dichotomous variables. This was followed by a multivariable logistic regression analysis including those variables with a p < 0.1 in the univariate analysis. A two-tailed P value of <0.05 was regarded as

significant. For analysis, we employed SPSS version 13.0 (SPSS Inc., Chicago, IL).

Results

A total of 100 patients were analyzed (Table 2). Mean patient age was 69.3 ± 8.9 years, and 59% (59) were male. Twenty-eight patients (28%) had GERD (GerdQ score ≥ 8). Clinical details of patients with and without GERD are compared in Table 2. Mean BW of patients with GERD was significantly higher than of those without GERD (P= 0.02). The proportion of patients receiving ARBs (46% vs. 69%; P=0.04) was significantly lower in the GERD group. In contrast, no significant difference was seen in the proportion of patients receiving CCBs (68% vs. 75%; P=0.47), while the proportion prescribed lipid lowering agents or oral glucose-lowering agents in the two groups was similar.

Multivariable logistic regression analysis was done using GERD-associated variables which had been found significant or marginally significant in the previous analysis (Table 2), with the presence or absence of GERD as the dependent variable. Results showed that BW (odds ratio (OR) 1.086; 95% confidence interval (CI): 1.020-1.157; P < 0.05) and ARB use (OR 0.302; 95% CI: 0. 112-0. 819; P < 0.05) were associated with the presence of GERD. SBP and diuretics uses were not significantly associated (Table 3).

Discussion

In this study, the prevalence of GERD in patients with ischemic

Investigation item	All patients (N=100)	GERD(+) (n=28)	GERD(-) (n= 72)	P-value
Age(year)	69.3±8.9	66.9±9.4	70.3±8.6	0.88
Gender(male/female)	59/41	17/11	42/30	1.00
Height(cm)	159.3±7.7	160.8±8.5	158.7±7.3	0.24
Body weight(kg)	62.8±10.1	67.8±12.8	60.2±9.1	0.02
Stroke type(A/L/C/T)	34/49/14/3	11/13/2/2	23/36/12/1	0.27
SBP(mmHg)	129.0±13.1	127.4±10.6	129.6±13.9	0.06
DBP(mmHg)	75.0±10.3	74.8±10.5	75.1±10.3	0.99
PR(/min)	69.7±10.8	70.5±10.4	69.4±11.0	0.46
Hypertension (%)	88(88)	23(82)	65(90)	0.31
ARBs (%)	63(63)	13(46)	50(69)	0.04
CCBs (%)	73(73)	19(68)	54(75)	0.47
Diuretics (%)	15(15)	1(4)	14(19)	0.06
ACEIs (%)	5(5)	2(7)	3(4)	0.62
Beta blockers (%)	7(7)	2(7)	5(7)	1.00
Alfa blockers (%)	7(7)	2(7)	5(7)	1.00
Dyslipidemia (%)	73(73)	13(64)	55(76)	0.32
Statins (%)	71(71)	19(68)	52(72)	0.81
Ezetimib (%)	2(2)	0(0)	2(3)	1.00
EPA (%)	12(12)	1(4)	11(15)	0.17
DM (%)	38(38)	14(50)	24(33)	0.17
SUs (%)	13(13)	4(14)	9(13)	0.75
DPP4 inhibitors (%)	24(24)	10(36)	14(19)	0.12
TDs (%)	13(13)	4(14)	9(13)	0.75
α-GIs (%)	7(7)	2(7)	5(7)	1.00
Insulin (%)	2(2)	1(4)	1(1)	0.48
Current smoking	5(5)	0(0)	5(7)	0.32

Values are mean ± standard deviation. Stroke type (A/L/C/T), atherothrombotic stroke/lacunar stroke, cardioembolic stroke/TIA; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; ACEIs, angiotensin converting enzyme inhibitors; SUs, sulfonylureas; DPP4 inhibitors, dipeptidyl Peptidase-4 inhibitors; TDs, thiazolidine derivatives; α-GIs, alfa-glycosidase inhibitors.

Table 2: Characteristics of Patients.

	Odds ratio	95% confidence interval	
		Lower limit	Upper limit
Body weight	1.086*	1.020	1.157
SBP	0.965	0.925	1.008
ARBs use	0.302*	0.112	0.819
Diuretics use	0.314	0.059	1.664

Odds ratios adjusted for age and sex.
*P<0.05, SBP, systolic blood pressure; ARBs, angiotensin receptor blockers.

Table 3: Odds ratios and 95% confidence intervals for independent predictors of GERD, identified by multivariable logistic regression analysis.

stroke as identified using the GerdQ questionnaire was 28%, which is higher than the approximately 10-20% prevalence previously reported in the general population [2,10]. This increase can be ascribed to the use of antiplatelet agents in these patients despite use of gastric coating agents. Ercelep et al. demonstrated that antiplatelet therapy was an independent risk factor for GERD symptoms [11]. Moreover, 16 patients were excluded from the present study owing to their use of proton pump inhibitors or H2 receptor antagonists for GERD symptoms within the previous month; inclusion of these patients would have increase the prevalence of GERD to approximately 38%. These findings highlight the need to protect patients with ischemic stroke from the development of GERD.

Our finding that BW was positively associated with the presence of GERD is consistent with a previous finding of a significant association with a body mass index (BMI) over 30 [11]. Recently, Niigaki et al. demonstrated that metabolic syndrome, a cluster of metabolic risk factors, was a significant predictive factor for the prevalence of GERD [12]. In contrast to our findings, however, they also found that subjects undergoing treatment for dyslipidemia and diabetes mellitus were at decreased risk of GERD. One reason for this difference might be the relatively young age of their participants, with a mean of 52 years versus our present subjects, at 69 years.

Hypertension is the single most important modifiable risk factor for recurrent stroke. Although blood pressure control is an important intervention for secondary stroke prevention [13], subjects undergoing treatment for hypertension are at increased risk of GERD [14]. The selection of antihypertensive drugs therefore requires consideration of digestive system function. In our subjects, use of either ARB or CCB was high, at 63% and 73%, respectively, while 52% received combination therapy. Among antihypertensive drugs, ARBs are considered to have greater efficacy in stroke prevention that CCB [15]. Generally, agents that relax the lower esophageal sphincter (LES) can induce GERD symptoms; CCBs in particular may decrease LES pressure and lead to the onset of GERD. In this regard, Horikawa et al. found that the prevalence of GERD was correlated with the proportion of patients treated with CCB on univariate correlation analysis, but found no significant association on logistic regression analysis, as in the present study [14].

The most intriguing result of our study was that the antihypertensive agent ARB was negatively associated with the presence of GERD. Multiple logistic regression analysis revealed that the combination of ARBs had a significant positive impact on endoscopic healing (OR 3.9, 95% CI 1.411-10.903), whereas no significant positive relationship was seen for other antihypertensive drugs such as CCBs.

Consistent with this finding, Miwa investigated endoscopic findings before and after treatment in 454 RE patients who received PPI therapy for 8 weeks and demonstrated that concomitant use of ARBs promoted endoscopic healing of RE in these patients [16]. Recently, Brzozowski

et al. reported a novel concept in the mechanism of protection of gastric mucosa by ARB [17]. They demonstrated a gastro-protective role of angiotensin-(1-7), an ANG II metabolite produced in the breakdown of ARBs. Angiotensin-(1-7) is produced in excessive amounts in the gastric mucosa and exhibits potent gastro-protective activity against gastric lesions. These findings provide evidence to support our results that ARB act as a protector to occurrence of GERD. ARBs appear to be better suited than CCBs for use in patients with ischemic stroke with regard to the prevention of GERD.

Limitations

Several limitations of the study warrant mention. First, sample size was small, which considerably limits the conclusions which can be drawn the data. A large number of prospective studies are required to confirm the result. Second, because there are no reports indicating association between GERD and ARB, it is not clear how ARB might protect the patients from GERD. Third, because the study was conducted under a cross-sectional design, we were unable to analyze the importance of the ARB-induced decrease in GERD. A comprehensive understanding of the relationship between ARBs and GERD prevalence awaits additional studies in a larger number of patients. One of ongoing study would yield some important findings with regard to the prevalence of gastrointestinal complications and related risk factors for low-dose aspirin users [18].

Acknowledgements

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