Vomiting should be a prompt predictor of stroke outcome

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ABSTRACT

Background To predict the outcome of stroke at an acute stage is important but still difficult. Vomiting is one of the commonest symptoms in stroke patients. The aim of this study is threefold: first, to examine the percentage of vomiting in each of the three major categories of strokes; second, to investigate the association between vomiting and other characteristics and third, to determine the correlation between vomiting and mortality.

Methods We investigated the existence or absence of vomiting in stroke patients in the Kyoto prefecture cohort. We compared the characteristics of patients with and without vomiting. We calculated the HR for death in both types of patients, adjusted for age, sex, blood pressure, arrhythmia, tobacco and alcohol use and paresis.

Results Of the 1968 confirmed stroke patients, 1349 (68.5%) had cerebral infarction (CI), 459 (23.3%) had cerebral haemorrhage (CH) and 152 (7.7%) had subarachnoid haemorrhage (SAH). Vomiting was seen in 14.5% of all stroke patients. When subdivided according to stroke type, vomiting was observed in 8.7% of CI, 23.7% of CH and 36.8% of SAH cases. HR for death and 95% CI were 5.06 and 3.26 to 7.84 ($p<0.001$) when all stroke patients were considered, 5.27 and 2.56 to 10.83 ($p<0.001$) in CI, 2.82 and 1.33 to 5.99 ($p=0.007$) in CH and 5.07 and 1.87 to 13.76 ($p=0.001$) in SAH.

Conclusions Compared with patients without vomiting, the risk of death was significantly higher in patients with vomiting at the onset of stroke. Vomiting should be an early predictor of the outcome.

INTRODUCTION

It is well known that vomiting is often seen at the onset of stroke even without accompanying nausea. It is more often seen in haemorrhagic stroke than in ischaemic stroke patients.[1 2] However, quantitative data on the frequency of vomiting at stroke onset remain unclear.[3 4] Causes may include brain swelling, increased intracranial pressure and meningeal stimulation.[5 6] Although it is not a specific symptom indicating the localisation, nor the exact nature of the lesion, it may be very important if it correlates with the outcome. As it is a finding noticeable by anyone, it may urge patients and their families to visit a doctor or call an ambulance. For paramedics and physicians as well, a prompt indicator of the severity of stroke is of great concern. Predicting the outcome of a stroke is important and much effort has been spent to determine major elements for predicting prognosis.[7 8] Arboix *et al*[9] reported nausea/vomiting as a predictor of early mortality for an ischaemic stroke in people without diabetes. However, the HR for death in stroke patients with vomiting, compared with that in patients without vomiting, has not been estimated. Predictors applicable in the clinical setting, particularly in the first 6 h of stroke onset, are not yet fully available.[10] Vomiting, although a non-specific symptom, is a good candidate for one of the predictors.

The aim of our study is to determine the following three points: first, the frequency of vomiting at stroke onset; second, differences in characteristics between patients who vomited at stroke onset and patients who did not; and third, whether vomiting is correlated with early stroke death.

If the occurrence of vomiting is high enough at stroke onset, it may be that vomiting is an important symptom as a prompt identifier at emergency care. Whether certain characteristics of stroke patients are related to vomiting or not is also of interest. It may give us additional information on the background, and, if mortality of patients with vomiting is higher than in patients without vomiting, this symptom could be a predictor of the stroke outcome.

METHODS

We have been continuing to register new stroke patients along with the data by clinician's findings at the first examination, patient's age, sex, present and past illnesses including hypertension, arrhythmia, diabetes mellitus and hyperlipaemia, smoking and drinking usages and patient's physical and mental conditions at a month after the admission. The registration is named the Kyoto Stroke Registry (KSR). Every citizen in Kyoto Prefecture regardless of age and sex is a subject of the KSR. Virtually all hospitals belonging to the Kyoto Medical Association have supported the KSR. Whether the patient is dead or alive is recorded up to 30 days after admission and, in the case of a patient's death within 30 days, survival time is recorded. Systolic hypertension is defined as 140 mm Hg or over and diastolic hypertension as 90 mm Hg or over. Any patient's history of hypertension, arrhythmia or diabetes mellitus is recorded, based on information given to the examining clinician by the patients themselves and/or their family, as well as on medical records and/or medicines that the patients had been taking. Vomiting was confirmed by local neurologists and/or neurosurgeons, based on the information given by the patients, and/or the people who were with the patients at the onset of stroke, and on first examination. Patients who were not confirmed to have been vomiting or not were excluded from this study. Vomiting at the onset of stroke

was defined as vomiting occurring as an initial symptom associated with the stroke event. Patients who vomited in the emergency room were also categorised as patients with vomiting. However, patients who first vomited after any medication and/or surgery at the hospital were regarded as patients without early vomiting in this study protocol in order to avoid confusion with patients with early vomiting.

The existence or absence of vomiting at onset was determined in 1968 new stroke patients from January 1999 to December 2000 in the Kyoto Prefecture cohort. Diagnosis of stroke was made by local neurologists and/or neurosurgeons together with the findings of CT (n=1778, 90.3%), MRI scans (n=1146, 58.2%), angiography (n=493, 25.1%) and scintigraphy for blood flow (n=253, 12.9%). Statistical analysis was performed in stroke as a whole and in three major subtypes: cerebral infarction (CI), cerebral haemorrhage (CH) and subarachnoid haemorrhage (SAH). Patients who were categorised as others, not fitting any one of the three subtypes, were excluded from further analysis.

The study was approved by the board of directors, the Kyoto Medical Association and by the Department of Health and Welfare, Kyoto Prefecture.

Statistical analysis

The differences in the frequencies of each characteristic among the three stroke types were examined with Pearson χ^2 analysis with Bonferroni correction for categorical characteristics and with Student's t test with Bonferroni correction for the numerical characteristics (age, systolic blood pressure and diastolic blood pressure). The statistical significance was set at $p<0.05$. The frequencies of vomiting among the three stroke types were determined and evaluated for univariate associations with Fisher's exact test. Age and systolic and diastolic blood pressure in the three types of stroke patients were compared with Student's t test. The OR for vomiting, comparing with and without each characteristic of stroke patients, was estimated by a logistic regression analysis. The Cox proportional hazards regression model was used to calculate age, sex, blood pressure and paresis-adjusted HR and their 95% CI for the risk of death of the patients with vomiting. Kaplan–Meier curves of estimated survival were generated, and comparisons between patients with vomiting and patients without vomiting were made using log-rank tests. Analysis was performed using SPSS V.19. All reported p values are two-sided.

RESULTS

The characteristics of the patients are summarised in table 1.

Of the 1968 confirmed stroke events in the study cohort, 1349 (68.5%) were CI, 459 (23.3%) were CH and 152 (7.7%) were SAH. A small number of patients had a combination of stroke types. Some had CI along with CH (n=3, 0.2%), or a combination of CI with SAH (n=3, 0.2%), or a combination of CH with SAH (n=2, 0.1%).

Vomiting was seen in 14.5% (286 out of 1968 patients) of all stroke patients. When subdivided into stroke types, vomiting was observed in 8.7% (118 out of 1349) CI patients, in 23.7% (109 out of 459) CH patients and in 36.8% (56 out of 152) SAH patients. Frequencies of systolic/diastolic hypertension at the medical examination were 78.2% (1516 out of 1939)/45.4% (875 out of 1927) when all stroke patients were considered, 76.7% (1022 out of 1333)/42.4% (564 out of 1329) in CI, 85.1% (383 out of 450)/54.3% (241 out of 444) in CH and 70.3% (104 out of 148)/44.5% (65 out of 146) in SAH. Data on vomiting, age and sex were complete in all patients in the study cohort. However, data on the other characteristics were missing in a few patients.

The characteristics of the patients with and without vomiting are summarised in table 2.

The characteristics of such in each stroke subtype are summarised in supplementary tables available online only (see supplementary table S2A–C).

The univariate factors statistically associated with vomiting were systolic and diastolic blood pressures, hypertension and arrhythmia histories, and paresis when all stroke patients were considered, systolic and diastolic blood pressure, hypertension history and paresis in CI, systolic and diastolic blood pressure and diabetes mellitus history in CH, and systolic and diastolic blood pressure and alcohol use in SAH. The OR for vomiting, comparing patients with and without a characteristic are summarised in table 3.

The OR in each stroke subtype are summarised in supplementary tables available online only (see supplementary table S3A–C).

A total of 1888 out of 1968 patients was confirmed to be alive or dead at 30 days after the stroke onset. A total of 193 out of 1888 patients (10.2%) died: 30.1% (83 out of 279) in patients with vomiting and 6.8% (110 out of 1612) in patients without vomiting. In CI, 5.9% (76 out of 1296) died: 16.7% (19 out of 114) in patients with vomiting and 4.8% (57 out of 1182) in patients without vomiting. In CH, 16.6% (73 out of 439) died:

Table 1 Characteristics of hospitalised stroke patients (n=1968)

	Overall (n=1968)	CI n=1349	CH n=459	SAH n=152
Vomiting, % (n)	14.5 (286/1968)	8.7 (118/1349)^{*1*2*3}	23.7 (109/459)^{*1*2*3}	36.8 (56/152)^{*1*2*3}
Age (SD)	71.1 (12.4)	72.6 (11.5)^{*1*2*3}	69.8 (13.1)^{*1*2*3}	62.0 (13.9)^{*1*2*3}
Sex, % female (n)	46.2 (910/1968)	42.3 (571/1349)^{*1*3}	52.5 (241/459)^{*1}	61.2 (93/152)^{*3}
Systolic blood pressure (SD)	162.2 (32.2)	159.1 (29.8)^{*1}	172.9 (35.0)^{*1*2}	158.1 (37.3)^{*2}
Diastolic blood pressure (SD)	87.7 (18.3)	86.3(16.5)^{*1}	92.2 (20.5)^{*1*2}	86.5 (23.9)^{*2}
Hypertension history, % (n)	60.1 (1092/1816)	58.4 (742/1270)^{*1*2*3}	69.8 (286/410)^{*1*2*3}	46.2 (60/130)^{*1*2*3}
Arrhythmia, % (n)	16.5 (313/1899)	20.7 (272/1311)^{*1*2*3}	7.7 (34/443)^{*1*2*3}	5.1 (7/137)^{*1*2*3}
Arrhythmia history, % (n)	19.6 (355/1813)	25.8(327/1269)^{*1*2*3}	5.9 (24/407)^{*1*2*3}	3.1 (4/129)^{*1*2*3}
Diabetes mellitus history, % (n)	21.8 (399/1832)	25.5(329/1290)^{*1*2*3}	15.2 (62/408)^{*1*2*3}	4.8 (6/126)^{*1*2*3}
Hyperlipaemia history, % (n)	18.2 (324/1784)	21.9 (276/1258)^{*1*2*3}	10.1 (40/395)^{*1*2*3}	5.7 (7/123)^{*1*2*3}
Tobacco use, % (n)	30.1 (488/1622)	31.4 (363/1155)^{*1*2*3}	22.7 (78/344)^{*1*2*3}	37.3 (44/118)^{*1*2*3}
Alcohol use, % (n)	40.0 (638/1594)	39.4 (442/1134)^{*3}	39.3 (133/338)^{*2}	52.6 (61/116)^{*2*3}
Paresis, % (n)	76.8 (1466/1909)	80.5 (1067/1326)^{*1*2*3}	81.4 (360/442)^{*1*2*3}	25.6 (34/133)^{*1*2*3}

Differences statistically significant between cerebral infarction (CI) and cerebral haemorrhage (CH), CH and subarachnoid haemorrhage (SAH) and SAH and CI were marked by ^{*1}, ^{*2} and ^{*3}, respectively. Data on some characteristics were missing in a few patients.

Table 2 Characteristics of patients with and without vomiting n=1968

	With vomiting (n=286)	Without vomiting (n=1682)	p Value
Age (SD)	68.9 (13.4)	71.4 (12.3)	0.002*
Sex, % female (n)	50.3 (144/286)	45.5 (766/1682)	0.140
Systolic blood pressure (SD)	176.1 (33.8)	159.9 (31.2)	<0.001*
Diastolic blood pressure (SD)	93.9 (21.6)	86.6 (17.5)	<0.001*
Hypertension history, % (n)	68.1 (173/254)	58.8 (919/1562)	0.006*
Arrhythmia, % (n)	12.5 (34/271)	17.1 (279/1628)	0.063
Arrhythmia history, % (n)	13.1 (32/244)	20.6 (323/1569)	0.005*
Diabetes mellitus history, %	19.8 (49/247)	22.1 (350/1585)	0.457
Hyperlipaemia history, % (n)	17.2 (40/233)	18.3 (284/1551)	0.716
Tobacco use, % (n)	26.6 (58/218)	30.6 (430/1404)	0.235
Alcohol use, % (n)	41.6 (91/219)	39.8 (547/1375)	0.656
Paresis, % (n)	65.1 (175/269)	78.7 (1291/1640)	<0.001*

*p<0.05.

35.5% (38 out of 107) in patients with vomiting and 10.5% (35 out of 297) in patients without vomiting. In SAH, 30.1% (44 out of 146) died: 50% (26 out of 52) in patients with vomiting and 19.1% (18 out of 94) in patients without vomiting.

The HR for death, comparing patients with vomiting and patients without vomiting are summarised in table 4.

As compared with patients without vomiting, the risk of death was significantly higher in patients with vomiting (HR and 95% CI were 5.06 and 3.26 to 7.84 (p<0.001) in overall stroke patients, 5.27 and 2.56 to 10.83 (p<0.001) in CI, 2.82 and 1.33 to 5.99 (p=0.007) in CH and 5.07 and 1.87 to 13.76 (p=0.001) in SAH, adjusted for age, sex, systolic blood pressure, diastolic blood pressure, arrhythmia, tobacco use, alcohol use and paresis.

Kaplan–Meier survival curves of stroke patients with and without vomiting are presented in figure 1. Kaplan-Meier survival curves in each stroke subtype are presented in supplementary figures available online only (see supplementary figure S1A-C). Figure 1(A) is for CI, (B) is for CH and (C) is for SAH (see supplementary figure 1A-C). Log-rank tests proved that the differences are statistically significant in overall stroke patients and in all three categories (p<0.001).

DISCUSSION

First, and most importantly, the HR adjusted for age, sex, systolic and diastolic blood pressures and paresis were high in patients with vomiting in stroke as a whole and in each three subtype of stroke. Kaplan–Meier survival curves showed that survival rates for the first 30 days after the event were worse in the patients with vomiting than in those without vomiting. Log-rank tests proved that those differences were statistically significant regardless of subtypes.

The findings suggest that vomiting at stroke onset could be a prompt predictor of early death after stroke. Vomiting is an outstanding symptom that is noticeable by patients' family and emergency care staff.[11] In contrast to other symptoms, such as headache and nausea, vomiting is a symptom that can be assessed even in patients with disturbed consciousness. Vomit is also often noticeable on patients' clothes. Patients who have vomited should be paid more attention immediately. Although vomiting cannot indicate the precise location or the nature of the lesion, such as ischaemic or haemorrhagic, it often suggests the massive effect of the lesion.[12] Vomiting should be a good candidate for predicting the outcome of a stroke applicable in a clinical setting, especially during the acute phase. The clinical usefulness of this, however, would depend on whether recognition of this as a poor prognostic indicator could lead to earlier treatment so that may improve the prognosis. Although this study did not cover the treatments, the relationship between vomiting at the onset of stroke and mortality should provide valuable information to identify patients who could benefit most from intensive care at the earliest stage. The emergency physician is advised to pay more attention to patients with vomiting and to try to prevent complications including aspiration pneumonia, which may be caused by vomiting.

Table 3 OR of vomiting, comparing with and without characteristics listed in the left column of the table (a logistic regression analysis), n=1968

	OR	95% CI	p Value
Age (70years or over)	1.17	0.81 to 1.71	0.404
Sex (female)	1.24	0.84 to 1.84	0.276
Systolic hypertension	1.95	1.12 to 3.40	0.019*
Diastolic hypertension	1.84	1.27 to 2.66	0.001*
Arrhythmia	1.82	0.75 to 4.40	0.186
Hypertension history	1.17	0.81 to 1.70	0.400
Arrhythmia history	0.36	0.15 to 0.84	0.018*
Diabetes mellitus history	0.89	0.58 to 1.38	0.604
Hyperlipaemia history	0.88	0.56 to 1.38	0.565
Tobacco use	0.69	0.44 to 1.08	0.108
Alcohol use	1.14	0.74 to 1.75	0.553
Paresis	0.38	0.26 to 0.55	<0.001*

Table 4 HR for death, comparing patients with vomiting and patients without vomiting

	HR	95% CI	p Value
Overall	5.06	3.26 to 7.84	<0.001*
Cerebral infarction	5.27	2.56 to 10.83	<0.001*
Cerebral haemorrhage	2.82	1.33 to 5.99	0.007*
Subarachnoid haemorrhage	5.07	1.87 to 13.76	0.001*

Adjusted for age, sex, systolic and diastolic blood pressure, arrhythmia, tobacco and alcohol use and paresis.

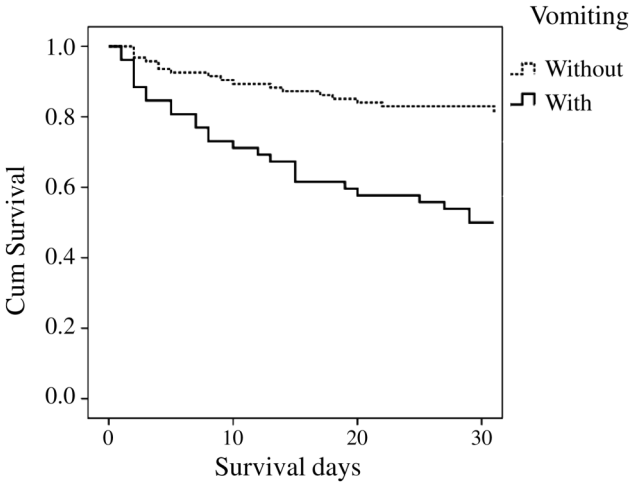

Figure 1 Kaplan–Meier survival curves of stroke patients with and without vomiting, p<0.001.

Second, the study showed the frequency of vomiting was different among stroke subtypes. Although vomiting is not a specific symptom for a certain type of stroke, it was more common in haemorrhagic than in ischaemic stroke, in agreement with previous investigations.[13 14] This study added the information that vomiting was about 1.5 times more frequently seen in SAH than in CH. The treatment of infarction, in which restoration of circulation is important, is the exact opposite to treating haemorrhage in which bleeding needs to be arrested. An obvious conclusion from this study is that vomiting should alert the emergency physician to the possibility of haemorrhage, because that is three to four times more likely to be the case, especially when CT or MRI is not available.

Third, we investigated the relations between vomiting and other characteristics of stroke patients. There was no significant difference in age and sex between the patients with vomiting and patients without vomiting. Both systolic and diastolic blood pressures were higher in patients with vomiting than in patients without vomiting, and this was most noticeable in haemorrhagic stroke. Vomiting showed an association with hypertension at the first examination but not with hypertension history. Causes of vomiting in stroke are not fully clarified, but may probably include brain oedema and/or increased intracranial hypertension, which may also elevate blood pressure.[15] Vomiting was more often seen in patients without paresis than in patients with paresis in CI.

Limitations

First, inherent limitations of the stroke registry for the entire prefecture are difficult to avoid. There may be missing data for stroke patients; for example, patients who died before arriving at hospitals and patients who went to hospital outside of the prefecture. Patients with mild symptoms might not have visited hospitals and patients with atypical symptoms might not have been diagnosed as such, and subsequently might not have been registered.

Second, we did not investigate the direct causes of death in this study. Viitanen *et al*[16] reported that the dominant causes of death, as verified by autopsy, were cerebrovascular disease in the first week, pulmonary embolism in the second to fourth week, bronchopneumonia during the second and third months and cardiac disease.

Third, vomiting could be influenced by meals, relapsed time after meals, and even transportation by ambulance.

With all these limitations, however, a significant bias that affects the major conclusion, that vomiting at the onset of stroke correlates with early mortality regardless of stroke subtype, is unlikely, because the study is based on a large cohort and this has sufficient statistical power.

CONCLUSIONS

Vomiting at the onset of stroke could be an indicator for higher death rate within 30 days after the stroke event and we should pay more attention to the symptom.

Contributors All authors contributed equally to this study.

Competing interests None.

Ethics approval Ethics approval was granted by the board of directors, the Kyoto Medical Association and by the Department of Health and Welfare, Kyoto Prefecture.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Runchey S,** McGee S. Does this patient have a hemorrhagic stroke?: clinical findings distinguishing hemorrhagic stroke from ischemic stroke. *JAMA* 2010;**303**:2280–6.
2. **Marti-Vilalta JL,** Arboix A. The Barcelona Stroke Registry. *Eur Neurol* 1999;**41**:135–42.
3. **Mohr JP,** Caplan LR, Melski JW, *et al*. The Harvard Cooperative Stroke Registry: a prospective registry. *Neurology* 1978;**28**:754–62.
4. **Feldmann E,** Gordon N, Brooks JM, *et al*. Factors associated with early presentation of acute stroke. *Stroke* 1993;**24**:1805–10.
5. **Oostenbrink R,** Moons KG, Donders AR, *et al*. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. *Acta Paediatrica* 2001;**90**:611–17.
6. **Krieger DW,** Demchuk AM, Kasner SE, *et al*. Early clinical and radiological predictors of fatal brain swelling in ischemic stroke. *Stroke* 1999;**30**:287–92.
7. **Saur D,** Ronneberger O, Kummerer D, *et al*. Early functional magnetic resonance imaging activations predict language outcome after stroke. Brain 2010;**133**:1252–64.
8. **Price CJ,** Seghier ML, Leff AP. Predicting language outcome and recovery after stroke: the PLORAS system. *Nat Rev Neurol* 2010;**6**:202–10.
9. **Arboix A,** Rivas A, Garcia-Eroles L, *et al*. Cerebral infarction in diabetes: clinical pattern, stroke subtypes, and predictors of in-hospital mortality. *BMC Neurol* 2005;**5**:9.
10. **Baron JC.** Stroke: predicting outcome after ischemic stroke-hard but achievable. *Nat Rev Neurol* 2011;**7**:253–4.
11. **Xiao B,** Wu FF, Zhang H, *et al*. Safety and efficacy of symptom-driven CT decision rule in fully conscious paediatric patients with symptoms after mild closed head trauma. *Emerg Med J* 2012. Epub Date 2012/02/16. DOI 10.1136/emermed-2011-200525
12. **Snider WD,** Simpson DM, Nielsen S, *et al*. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann Neurol* 1983;**14**:403–18.
13. **Yock-Corrales A,** Mackay MT, Mosley I, *et al*. Acute childhood arterial ischemic and hemorrhagic stroke in the emergency department. *Ann Emerg Med* 2011;**58**:156–63.
14. **Rendell S,** Batchelor JS. An analysis of predictive markers for intracranial haemorrhage in warfarinised head injury patients. *Emerg Med J* 2012. Epub Date 2012/03/01. DOI 10.1136/emermed-2011-200176
15. **Bouma GJ,** Muizelaar JP, Bandoh K, *et al*. Blood pressure and intracranial pressure-volume dynamics in severe head injury: relationship with cerebral blood flow. *J Neurosurg* 1992;**77**:15–19.
16. **Viitanen M,** Winblad B, Asplund K. Autopsy-verified causes of death after stroke. *Acta Medica Scandinavica* 1987;**222**:401–8.

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