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Off-Hour Admission and Outcomes in Patients with Acute Intracerebral Hemorrhage in the INTERACT2 Trial

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Intracerebral hemorrhage · Hypertension · Blood pressure · Acute stroke care · Clinical trials

Abstract
Background: Conflicting data exist of an association between off-hour (weekend, holiday, or night-time) hospital admission and adverse outcome in intracerebral hemorrhage (ICH). We determined the association between off-hour admissions and poor clinical outcome, and of any differential effect of early intensive blood pressure (BP) lowering treatment between off- and on-hour admissions, among participants of the Intensive BP Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2). ***Methods:*** Subsidiary analysis of INTERACT2, a multinational, multicenter, clinical trial of patients with spontaneous ICH with elevated systolic BP, randomly assigned to intensive (target systolic BP <140 mm Hg) or guideline-based (<180 mm Hg) BP management. Primary outcome was death or major disability (modified Rankin scale of 3–6) at 90 days. Off-hour admission was defined as night-time (4:30 p.m. to 8:30 a.m.) on weekdays, weekends (Saturday and Sunday), and public holidays in each participating country. ***Results:*** Of 2,794 patients with information on the primary outcome, 1,770 (63%) were admitted to study centers during off-hours. Off-hour admission was not associated with risk of poor outcome at 90 days (53% off-hour vs. 55% on-hour; p = 0.49), even after adjustment for comorbid risk factors (odds ratio 0.92; 95% CI 0.76–1.12). Consistency exists in the effects of intensive BP lowering between off- and on-hour admission (p = 0.85 for homogeneity). ***Conclusions:*** Off-hour admission was not associated with increased risks of death or major disability among trial protocol participants with acute ICH. Intensive BP lowering can provide similar treatment effect irrespective of admission hours.

For a full list of INTERACT2 Investigators, see online supplementary material.

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Introduction

Stroke patients who were admitted to the hospital on a weekend, in the night or during holidays [1–8], have been reported to have higher mortality compared to those admitted during the usual business hours of hospitals. This phenomenon is called 'weekend effect' or 'off-hour effect'. However, several studies report no such differences in outcome between off-hour and on-hour admission [9–11], particularly within coordinated specialist care systems such as for comprehensive stroke centers [12, 13] and/or following the implementation of stroke care pathways in the community [14], Because evidence for the 'off-hour effect' is mainly derived from patients with acute ischemic stroke [15], there is uncertainty about any such association in patients with acute intracerebral hemorrhage (ICH) [2, 6, 11, 14, 16]. The objectives of our study were first, to elucidate the association of off-hour admission with poor clinical outcomes in over 2,800 patients with acute ICH using data from the main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) [17, 18]; and second, to compare the effects of early intensive blood pressure (BP) lowering between patients who were admitted during off-hours and those admitted on-hours.

Methods

Study Design and Participants

This is a post-hoc analysis of the INTERACT2 study, an international, multicenter, open, blinded endpoint, randomized controlled trial, which has been described in detail elsewhere [17, 18]. In brief, 2,839 patients with spontaneous ICH within 6 hours of onset and elevated systolic BP (SBP 150–220 mm Hg) were enrolled from 144 mainly urban tertiary referral hospitals in 21 countries between October 2008 and August 2012. Patients were centrally randomly assigned to receive intensive (target SBP <140 mm Hg within 1 h) or guideline-recommended (target SBP <180 mm Hg) BP-lowering therapy. The study protocol was approved by the appropriate ethics committee at each participating site and written informed consent was obtained directly from the patient or from an appropriate surrogate.

Procedures

Off-hour was defined as night-time (4:30 p.m. to 8:30 a.m.) on weekdays, weekends (Saturday and Sunday), and public holidays in each country. Demographic and clinical characteristics were recorded at the time of enrollment. Stroke severity was measured using the Glasgow Coma Scale (GCS) and National Institutes of Health stroke scale (NIHSS) at baseline. Countries were classified as high-, low- or middle-income countries according to the World Bank's classification [19].

Outcomes

The primary outcome was death or major disability (defined by scores 3–6 on the modified Rankin scale (mRS)) at 90 days. Secondary outcomes were death (mRS score 6) and major disability (mRS scores 3–5) separately.

Statistical Analysis

Baseline characteristics and stroke management during the first 7 days were summarized as mean (SD) or median (IQR) for continuous variables, and as number (%) for categorical variables according to patient groups defined by time of admission (off-hour and on-hour). The differences between the two groups were tested using Kruskal-Wallis test for continuous variables and Chi-square test for categorical variables. The association of off-hour admission on clinical outcomes was estimated using logistic regression models. Variables were included in the adjusted model if they were either significant in univariable analysis (prior treatment for hypertension, use of antithrombotic therapy, use of lipid lowering therapy, time from onset to admission, SBP, low (≤8) GCS score, glucose level, admission to an intensive care unit, prophylactic treatment against venous thromboembolism, and use of intravenous mannitol) or pre-specified variables determined to be clinically important (age, sex, country (high income vs. low/middle income), baseline hematoma volume, lobar location of hematoma, intraventricular extension, and randomized treatment). We also developed models for each outcome at 90 days with country, GCS, use of intravenous mannitol, any surgical intervention, and admission to an intensive care unit, and showed the results as supplemental information (online suppl. fig. A–E; for all online suppl. material, see www.karger.com/doi/10.1159/000434690). The effects of early intensive BP lowering on the primary outcome were also assessed by logistic regression models. Comparisons of treatment effects between the 2 patient groups were performed by adding an interaction term to the statistical model. A standard level of significance ($p < 0.05$) was used and the data were reported with odds ratios (OR) and 95% confidence intervals (CI). Given the rate of death or major disability of 55% in the on-hour group, the present analysis with sample size of 1,024 in the on-hour group and 1,770 in the off-hour group had 80% power (2-sided alpha = 0.05) to detect more than 10% relative increase in the outcome. All data were analyzed with the use of SAS software (version 9.3).

Results

Baseline Characteristics and Treatment

Among 2,839 participants of the INTERACT2 cohort, 2,794 with information on mRS at 90 days were included in the present analysis (excluding 45 patients (8, no consent obtained; 2, no data obtained; and 35, unavailable mRS)). A total of 1,770 (63%) patients were admitted during off-hours. Table 1 indicates that patients with off-hour admission were younger, more likely to be enrolled in low- or middle-income countries, and less likely to have had prior antihypertensive, antithrombotic and lipid-lowering therapy. They also had

Table 1. Baseline characteristics of participants by time of admission

	Total (n = 2,794)	On-hour (n = 1,024)	Off-hour (n = 1,770)	p
Demographic				
Age, years	64 (13)	65 (13)	63 (13)	<0.0001
Female	1,041 (37)	366 (36)	675 (38)	0.22
Low/middle income countries	2,031 (73)	666 (65)	1,365 (77)	<0.0001
Medical history				
Intracerebral hemorrhage	226 (8)	80 (8)	146 (8)	0.74
Ischemic stroke	283 (10)	96 (9)	187 (11)	0.35
Acute coronary syndrome	79 (3)	36 (4)	43 (2)	0.12
Hypertension	2,021 (72)	741 (72)	1,280 (72)	1.00
Diabetes	300 (11)	118 (12)	182 (10)	0.34
Medication history				
Antihypertensive therapy	1,255 (45)	486 (48)	769 (44)	0.04
Oral anticoagulation therapy	81 (3)	41 (4)	40 (2)	0.01
Antiplatelet therapy	261 (9)	110 (11)	151 (9)	0.06
Antithrombotic therapy	330 (12)	148 (14)	182 (7)	0.001
Lipid lowering therapy	197 (7)	91 (9)	106 (6)	0.005
Clinical features				
Median time from onset to admission, h	1.42 (0.85–2.25)	1.50 (1.00–2.47)	1.33 (0.83–2.08)	<0.0001
Median time from onset to imaging, h	1.78 (1.20–2.68)	1.87 (1.25–2.88)	1.73 (1.15–2.58)	0.002
Median time from onset to randomization, h	3.73 (2.81–4.71)	3.82 (2.81–4.81)	3.66 (2.81–4.64)	0.10
Systolic BP, mm Hg	179 (17)	178 (17)	180 (17)	0.01
Diastolic BP, mm Hg	101 (15)	100 (15)	102 (15)	0.0003
Median GCS score	14 (12–15)	14 (13–15)	14 (12–15)	<0.0001
GCS score ≤8	165 (6)	37 (4)	128 (7)	<0.0001
Median NIHSS score	11 (6–16)	10 (6–15)	11 (6–16)	0.18
NIHSS score ≥14	933 (34)	336 (33)	597 (34)	0.61
Glucose, mmol/l	7.2 (2.6)	7.0 (2.4)	7.2 (2.7)	0.048
CT findings				
Median hematoma volume, ml	11.0 (5.8–19.5)	10.7 (5.9–19.9)	11.2 (5.8–19.0)	0.98
Hematoma location				0.02
Lobar	253 (9)	111 (11)	142 (8)	
Deep	2,149 (77)	785 (77)	1,364 (77)	
Cerebellar	88 (3)	22 (2)	66 (4)	
Brain stem	79 (3)	27 (3)	52 (3)	
Intraventricular extension	730 (28)	261 (28)	469 (29)	0.55
Randomized intensive BP lowering therapy	1,382 (49)	499 (49)	883 (50)	0.58

Data are n (%), mean (SD), or median (interquartile range). p values are based on Chi-squared or Kruskal-Wallis test. CT = Computed tomography. Low/middle income countries are China (n = 1,909), India (n = 92), Pakistan (n = 9), Argentina (n = 4), and Brazil (n = 17).

shorter onset to admission time, higher BP and glucose levels, and lower GCS scores, at baseline. Table 2 shows details of their acute stroke care during the first 7 days post-randomization. Patients with off-hour admission were more likely to have been admitted to an intensive care unit and receive intravenous mannitol, but less likely to have had prophylactic venous thromboembolism treatment.

Off-Hour Admission and Clinical Outcomes

A total of 1,504 patients died or had residual major disability at 90 days. Table 3 shows the associations between off-hour admission and clinical outcomes. Off-hour admission did not increase the risk of death or major disability at 90 days (53% for off-hour vs. 55% for on-hour; p = 0.49). There were no significant associations after adjustment for various baseline risk factors and clinical features:

Table 2. Acute stroke care by time of admission

	Total (n = 2,794)	On-hour (n = 1,024)	Off-hour (n = 1,770)	p
During the first 24 h				
Number of oral antihypertensives	1 (0–1)	1 (0–1)	1 (0–1)	0.11
Number of intravenous antihypertensives	1 (0–1)	1 (0–1)	1 (0–1)	0.32
During the first 7 days*				
Intubation	186 (7)	71 (7)	115 (7)	0.74
Admission to an intensive care unit	1,049 (38)	359 (36)	690 (40)	0.03
Prophylactic treatment for deep-vein thrombosis	594 (22)	259 (26)	335 (19)	0.0001
Compression stockings	287 (10)	123 (12)	164 (9)	0.03
Subcutaneous heparin	479 (17)	209 (21)	270 (16)	0.0007
Use of intravenous mannitol	1,707 (62)	549 (54)	1,158 (67)	<0.0001
Hemostatic therapy	97 (4)	40 (4)	57 (3)	0.41
Any surgical intervention	153 (6)	52 (5)	101 (6)	0.52
Evacuation or decompression of the hematoma	81 (3)	26 (3)	55 (3)	0.44
Insertion of a ventricular drain	84 (3)	30 (3)	54 (3)	0.93
Decision to withdraw active treatment and care	120 (4)	44 (4)	76 (4)	1.00

Data are n (%) or median (interquartile range). p values are based on Chi-squared or Kruskal-Wallis test. * 50 patients' data were unavailable.

Table 3. Effects of off-hour admission on clinical outcomes

	On-hour (n = 1,024)	Off-hour (n = 1,770)	p
Death or major disability			
Number of outcomes, %	560 (55)	944 (53)	
Crude OR	1 (ref.)	0.95 (0.81–1.11)	0.49
Adjusted OR*	1 (ref.)	0.92 (0.76–1.12)	0.40
Death			
Number of outcomes, %	115 (11)	221 (12)	
Crude OR	1 (ref.)	1.13 (0.89–1.43)	0.33
Adjusted OR*	1 (ref.)	1.29 (0.94–1.77)	0.12
Major disability			
Number of outcomes, %	445 (43)	723 (41)	
Crude OR	1 (ref.)	0.90 (0.77–1.05)	0.18
Adjusted OR*	1 (ref.)	0.86 (0.72–1.03)	0.11

Ref. = Reference. * Adjustment for age, sex, country (high income vs. low/middle income), treated hypertension, antithrombotic therapy, lipid lowering therapy, time from onset to admission, systolic blood pressure, glucose, low (8 or less) Glasgow Coma Scale score, baseline hematoma volume, lobar location of hematoma, intraventricular extension, randomized treatment, admission to an intensive care unit, prophylactic treatment against venous thromboembolism, and use of intravenous mannitol.

OR 0.92 (95% CI 0.76–1.12) for off-hour admission compared to the on-hour admission patients. Similarly, no clear associations were observed for death (multivariable-adjusted OR 1.29 (95% CI 0.94–1.77)) or major disability (multivariable-adjusted OR 0.86 (95% CI 0.72–1.03)).

Sensitivity Analysis

Off-hour admission was associated with death in low- or middle-income countries in the crude model (OR 1.45 (95% CI 1.04–2.01)) (online suppl. table A). However, the relationship was not significant after adjustment (OR 1.37 (95% CI 0.88–2.13)). There was a significant relationship between off-hour admission and higher mortality in patients who received any surgical treatment during the first 7 days (OR 2.94 (95% CI 1.13–7.65)). The association remained after adjustment for various management factors (OR 25.82 (95% CI 2.40–278.15)) (online suppl. table D).

Because Saturday is counted as a weekday in some countries, with the same resources/staff as in other week days, we did an analysis using Saturday as a weekday. In addition, we did an analysis using different night-time definition (7:00 p.m. to 7:00 a.m.). These analyses produced similar results: frequencies of death or major disability at 90 days were 53% for off-hour vs. 55% for on-hour (multivariable-adjusted OR 0.94 (95% CI 0.78–1.14)) and 52% for off-hour vs. 55% for on-hour (multivariable-adjusted OR 0.87 (95% CI 0.72–1.05)), respectively.

Effects of Randomized Intensive BP Lowering

Figure 1 shows that there were no significant differences in the magnitude of the therapeutic effects of intensive BP lowering on death or major disability at 90 days between off- and on-hour admission: OR 0.86 (95% CI 0.71–1.03) and OR 0.88 (95% CI 0.69–1.13), respectively

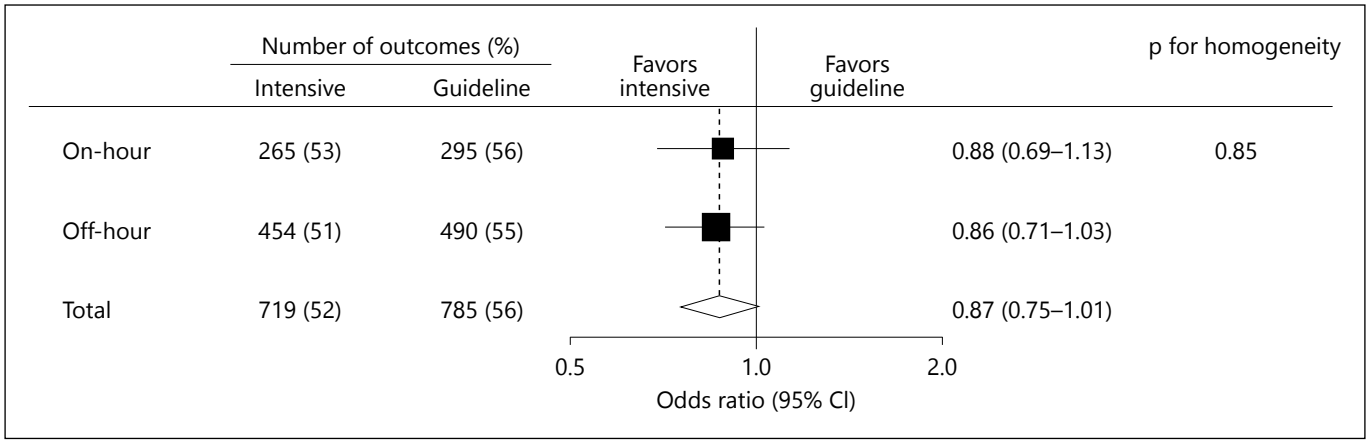

Fig. 1. Effects of intensive blood pressure lowering on death or major disability. Solid boxes represent estimates of treatment effect; horizontal lines, 95% CI; a diamond, the estimate and 95% CI for overall effect. Areas of the boxes are proportional to inverse variance of estimates.

(p = 0.85 for homogeneity). There were also no significant differences in the therapeutic effects on ordinal mRS outcome between off- and on-hour admission: OR 0.87 (95% CI 0.74–1.03) and OR 0.88 (95% CI 0.71–1.09), respectively (p = 0.97 for homogeneity) (online suppl. fig. A).

Discussion

These analyses of the INTERACT2 trial, which included over 2,800 patients, demonstrated that off-hour hospital admission was not associated with increased risks of death or major disability. These data also indicated that intensive BP-lowering treatment was likely to provide comparable benefits for patients with ICH, regardless of admission hours.

A number of observational studies have investigated the 'off-hour effect' in patients with acute ICH. Analysis of 13,821 acute ICH patients using the 2004 Nationwide Inpatient Sample Dataset of the United States found that weekend admission was associated with significantly higher in-hospital mortality than admission on weekdays [2]. Similarly, the United States 'Get with the Guidelines-Stroke' program demonstrated increased in-hospital mortality associated with off-hour (weekends and holidays) admission among 34,845 patients with acute ICH [6]. However, analysis of 10,987 ICH patients from the Canadian Hospital Discharge Database showed no significant difference of in-hospital mortality between weekend and weekday admission [16]. Discrepancies across studies may be attributable to differences in the availability of organized specialist stroke care, defined by the use of stroke units [20, 21], quality of care checklists [5], and patient-staff ratio [3] during off-hours. In the present analysis of INTERACT2, where all participants received a standardized treatment protocol and background management according to best practice acute stroke care [17, 18], there was no difference in outcome between off- and on-hour admission. Our results supported the hypothesis that 24 h standardized stroke care at monitored facilities can overcome any off-hour variation in effect.

In this study, patients with off-hour admission were less likely to have had prior antihypertensive, antithrombotic and lipid-lowering treatment, and also had lower GCS scores. This may be partly due to difficulty in obtaining an accurate history in off-hour, especially in patients with lower consciousness levels. Even though there could have been external factors causing these differences in baseline characteristics, it seems to suggest that patients who were critically ill were more likely to be admitted to stroke centers during off-hours. Intriguingly, off-hour admission was related to greater risk of death at 90 days in patients receiving any surgical intervention within 7 days. Though off-hour admission might affect decision-making over the indication of surgery and/or postoperative care, the strength of evidence is limited by the small number of clinical events.

The main results of the INTERACT2 study provide support for early intensive BP-lowering treatment to improve functional outcomes without any increase in mortality or serious adverse events in patients with acute ICH [17, 18]. In this study, there was no evidence of heterogeneity in the effects according to the time of day for the initiation of treatment. Thus, intensive BP lowering is

likely to be a generalizable treatment strategy irrespective of admission hours among patients with acute ICH under assuring background stroke care.

Beyond our expectation, the median time from onset to admission, imaging, and randomization were relatively shorter in off-hour patients than on-hour patients in the present analysis. This could be referred to as the 'reverse off-hour effect'. Similar associations have been observed in other studies. A study of 20,657 patients admitted to 11 Canadian stroke centers reported that patients presented on weekends were more likely to be transported to the hospital by ambulance, had a shorter time from stroke onset to hospital arrival and shorter time from arrival to neuroimaging, and were more likely to have a moderate or severe stroke rather than a mild stroke compared to those who presented on weekdays [4]. A Chinese study from a hospital-based stroke registry (ChinaQUEST) [22] found that factors that accelerated presentation to the hospital included decreased level of consciousness (GCS score ≤8) and transfer by ambulance. The study also reported factors associated with prolonged time to presentation including visit to a local doctor before presenting at emergency department. Our patients with off-hour admission also had lower level of consciousness. Although data regarding prehospital pathways are not available in INTERACT2, we can speculate that access to local doctors could be limited during off-hour, and therefore, more stroke patients presented at participating centers earlier than on-hour. Increase in neuroimaging availability due to lack of planned examinations during off-hour, which may contribute to reduction in admission to imaging time and lower consciousness level could also affect neuroimaging prioritization.

Strengths of the present analysis included the large sample size and heterogeneous patient population with early rigorous prospective evaluations after acute ICH. Another positive factor about this study is that we systematically collected information on participant characteristics including stroke severity and included them in the multivariable analyses, which have not been possible in many previous studies due to the small number of participants. However, there were also some limitations. To begin with, the present analysis was prone to bias and confounding as it was post-hoc, observational and not pre-specified. One possible reason why there was no difference in outcome between off- and on-hour admission was that patients were recruited and managed in well-organized stroke centers by virtue of participation in a randomized controlled trial, with indirect benefits into patient care such as through more rapid assessment and treatment, and more intensive monitoring than is typical for most ICH patients. These differences in clinical setting might also limit the generalizability of results. Another factor is that we were unable to assess aspects of the organization of care, such as hospital size and the expertise and numbers of staff, which have influenced outcome from ICH. Finally, our findings may not be applicable to cases of severe ICH which were purposely excluded from participation in INTERACT2, despite our finding of no differences in neurosurgical intervention between off- and on-hour groups of patients.

Conclusions

Off-hour admission was not associated with poor outcome in patients with acute ICH who participated in the INTERACT2 trial. We suggest that early intensive BP lowering provides similar therapeutic effect irrespective of admission hours. Disadvantage of off-hour admission may be avoidable when stroke care is standardized and based in 24-hour monitored facilities.

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