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Current management of subarachnoid hemorrhage in a northern urban Chinese population: a multi-center surveillance study

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Abstract. – OBJECTIVE: The current management of subarachnoid hemorrhage (SAH) in the urban Chinese population remains unclear and the relevant literature is still lacking. Therefore, this work aimed to investigate the recent clinical practice in the management of spontaneous SAH in an urban population-based setting.

PATIENTS AND METHODS: From 2009 to 2011, the China Epidemiology Research In Subarachnoid Hemorrhage (CHERISH) project, which was a two-year prospective, multi-center, population-based, case-control study, was performed in the northern urban Chinese population. SAH cases were described in terms of their features, clinical management, and in-hospital outcomes.

RESULTS: Totally of 226 cases were enrolled with a final diagnosis of primary spontaneous SAH (65% of females; mean age, 58.5±13.2 years; range, 20-87 years). Among them, 92% of these patients received nimodipine, while 93% took mannitol. Meanwhile, 40% of them received traditional Chinese medicine (TCM), while 43% took neuroprotective agents. Endovascular coiling was applied in 26% of 98 angiography-confirmed intracranial aneurysms (IA) cases, while neurosurgical clipping was in 5% of them.

CONCLUSIONS: Our findings on the management of SAH in the northern metropolitan Chinese population reveal that nimodipine is an effective medical therapy with a high rate of use. There is also a high utilization rate of alternative medical interventions. Endovascular coiling occlusion is more common than neurosurgical clipping. Therefore, regionally traditional therapy may be a key factor for the difference in the treatment of SAH between northern and southern China.

Key Words:
Subarachnoid hemorrhage, Nimodipine, Clinical management, Traditional Chinese medicine, Neurosurgical intervention.

Introduction

Subarachnoid hemorrhage (SAH) is a rare, but the most devastating type of stroke[1]. It is caused by the rupture of an intracranial aneurysm (IA). Notably, aneurysmal SAH is the deadliest type of SAH, with a 1-month case fatality rate of 35% in developed countries[2]. Furthermore, one-third of survivors require lifelong care, and another third has a cognitive impairment that impairs their function and quality of life[2]. IA-related SAH can cause a sudden increase in intracranial pressure and sympathetic outflow, resulting in abrupt mortality, unconsciousness, and cardiac problems. Due to the improved diagnostic and therapeutic procedures for SAH[3,4], organized care[5], and endovascular coiling of ruptured IA[6], the global incidence of SAH has decreased by approximately 0.6% per year since 1998[7]. Nevertheless, due to geographical and medical differences, the incidence tends to be higher in northern China (approximately 6.2 per 100,000 people per year) than that in central and southern China[8]. Meanwhile, SAH remains a highly fatal condition with a 30-day mortality rate of up to 35%[9,10].

As a neurologic emergency, SAH requires prompt diagnosis and management to prevent life-threatening rebleeding as well as to optimize patient outcomes. However, there are few published studies concerning SAH management in China, particularly on the treatment patterns that reflect local customs and practices rather than guidelines. At the same time, there is a scarcity of population-based data on the clinical management of SAH in this region. Further understanding of the management of SAH in China can contribute to improving the diagnostic and therapeutic procedures of SAH. Therefore, this population-based study aimed to investigate the current patterns of in-hospital therapy of

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SAH, which encompassed medicinal, surgical, and endovascular treatments in a northern urban Chinese population.

Patients and Methods

Participants and Setting

The China Epidemiology Research In Subarachnoid Hemorrhage (CHERISH) project was a prospective, population-based, multicenter, case-control study conducted in the complete urban area defined by the 4 districts of Kundulun, Qingshan, Jiuyuan, and Donghe of Baotou, the largest city in Inner Mongolia, China during 2009-2011. According to the 2010 National Census[11], Baotou had a relatively consistent and moderate-size non-immigrant population estimated at 1.82 million (≥15 years of age). The Chinese hospitals were classified as Level 1 community hospitals with only the most basic facilities and very limited inpatient capacity, Level 2 hospitals with at least 100 inpatient beds providing acute medical care and preventative care services to at least 100,000 people, and Level 3 major tertiary referral centers in provincial capitals and major cities. Meanwhile, there was a network of all the major acute care hospitals with neurology/neurosurgery capabilities and CT scanners (including nine Level 3 and two Level 2 hospitals), one army hospital, minor hospitals (including three Level 1 hospital with CT scanners), and the city's solitary crematorium. Structured face-to-face interviews were undertaken on cases as soon as possible after notification in order to collect data on social demographics, lifestyle, and medical history. At the same time, information concerning clinical features, care, and in-hospital outcomes was obtained from neurologists.

Inclusion and Exclusion Criteria

All adult (≥15-years) cases of spontaneous SAH due to presumed rupture of IA are included among residents of the study area for 2 years from 8 May 2009. SAH is defined according to standard criteria[12] as an abrupt onset of severe headache and/or loss of consciousness (with/without focal neurological signs), with evidence of focal or generalized blood in the subarachnoid space confirmed by computed tomography (CT), necropsy, or lumbar puncture. Patients with SAH secondary to arteriovenous malformations, trauma, or neoplasm were excluded. Digital pictures of CT and angiographic findings on each case are transmitted by e-mail to the central coordinating center for confirmation of the diagnosis.

Statistical Analysis

Categorical data were expressed as proportions, while continuous variables were represented by means with standard deviation (SD) or median with interquartile range by data distribution. Patient sociodemographic characteristics, clinical features, and history of concomitant cardiovascular risk factors were all included in the baseline information. In addition, diagnostic and management approach employed in hospitals, including neuroimaging, intravenous/oral medications, supportive care, and neurosurgery clipping or endovascular coiling, were also summarized. The specific in-hospital outcomes including complications [like pneumonia, urinary tract infection, pulmonary embolus, coronary event, seizure, symptomatic hydrocephalus, symptomatic cerebral vasospasm (CVS), falls with injury, other sepsis, or any other clinically significant event that extended the length of hospital stay], modified Rankin Scale (mRS) score, death, and discharge destination were also presented.

The study protocol was approved by the Ethics Committees of the University of Sydney and Baotou Central Hospital. Besides, informed consent was obtained from the subjects or an appropriate proxy.

Results

In total, there were 688 SAH cases registered over the study period, as shown in Figure 1. Among them, 160 were excluded either because they were not residents of the study area or were not diagnosed with SAH. Typically, SAH was diagnosed in 528 patients including 6 who suffered from an arteriovenous malformation (AVM), 282 from secondary head trauma, and 11 from other causes. Moreover, three individuals had recurrence episodes over the study period and withdrew from the research.

Thus, a total of 226 cases were registered with a final diagnosis of primary spontaneous SAH (65% of females; mean age, 58.5±13.2 years; range, 20-87 years). The characteristics of these 226 SAH patients are shown in Table I. According to our analysis, SAH patients tended to be middle-aged and had a history of hypertension before admission, around two-thirds of them

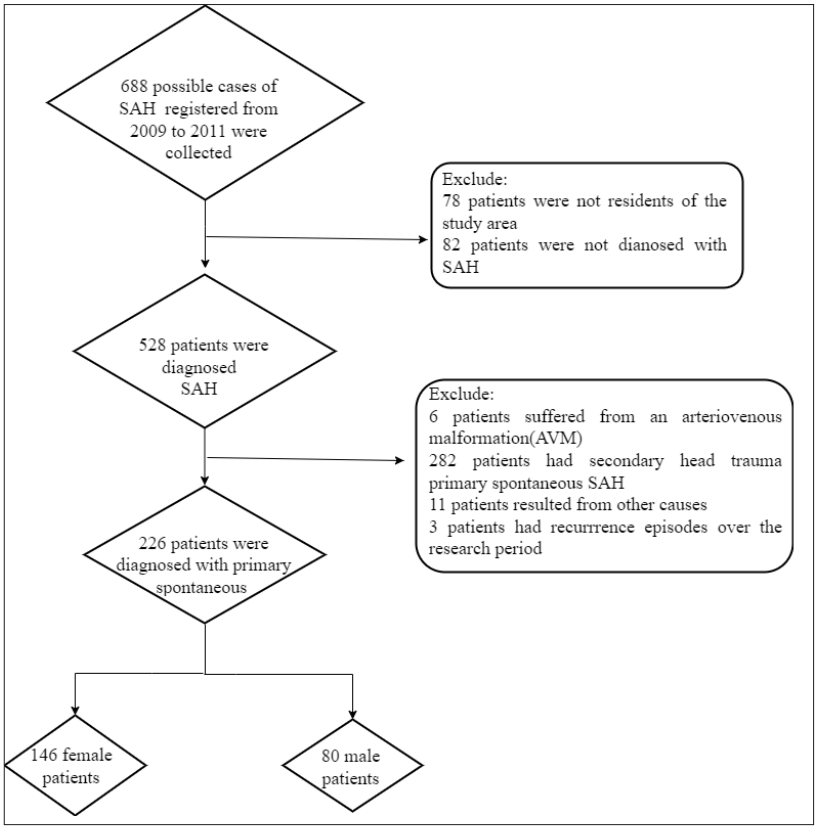

Figure 1. Flow chart of the research population screening.

were presented within 6 hours after symptom onset, and there were most patients with Hunt and Hess scale ≥ 3.

Table II presents the management and in-hospital outcomes of SAH patients. During the length of hospital stay, 45 patients died (20%). Approximately 1/5 of survivors were reported as being disabled/dependent at the time of hospital discharge. However, the modified Rankin Scale scores of these disabled/dependent survivors at discharge were 0-2 on the scale. Besides, intravenous and/or oral nimodipine, intravenous traditional Chinese medicine (TCM), various neuroprotectant agents (such as intravenous edaravone, ganglioside GM1, cattle encephalon glycoside, and cinepazide, citicoline), haemodilution agents (like mannitol), and intravenous tranexamic acid were all heavily used among the various management options. Nimodipine was administered in 92% of the 266 patients, while mannitol was given to 93% of them. Meanwhile, intravenous tranexamic acid was used in 73% of the patients, while TCM and neuroprotective agents were used in 40% and 43% of them, respectively. Endovascular coiling was used in 26% of the 98 patients with angiography-confirmed IA, whereas neurosurgical clipping was conducted in 5% of these cases. Due to financial constraints, 33 patients (34%) with IA did not receive either endovascular coiling or neurosurgical clipping. The great majority of patients were managed in the hospital during the acute phase, where SAH was confirmed by CT or MRI in all patients.

Discussion

Patients need to be evaluated in a high-volume center as soon as SAH is identified. The emergency physician and neurologist should consider the initial management issues including airway, blood pressure control, administration of analgesics, cardiac monitoring, vasospasm treatment, anticoagulation reversal, and seizure treatment in

Table I. Baseline characteristics of SAH patients.

	Total (N = 226)
Sociodemographic	
Age, mean (SD), years	58.5 ± 13.2
Female	146 (65)
Living alone	9 (4)
High education (≥ university)	31 (14)
Insurance	191 (88)
Han ethnicity	206 (93)
Full-time paid work before the SAH	46 (21)
Main lifetime occupation type	
Manual work[†]	57 (26)
None reported	47 (21)
Financial situation	
Not enough money to get along	12 (5)
None reported	1 (0)
Medical history	
History of hypertension	110 (50)
History of diabetes mellitus	22 (10)
History of hyperlipidemia	23 (10)
Prior stroke	29 (13)
Prior coronary artery disease[‡]	20 (9)
Current smoker	67 (31)
Regular alcohol consumption[§]	39 (18)
Overweight[‖]	101 (46)
Medication history (within one month of SAH onset)	
Antihypertensive	84 (40)
Antiplatelet	22 (10)
Warfarin	0 (0)
Lipid-lowering	6 (3)
Clinical features	
Time from symptom onset to hospital presentation	
Median (IQR), hours	1.5 (0.5, 9.5)
< 6 hours	147 (71)
Transported to hospital by ambulance	134 (60)
Poor GCS score on admission[#]	53 (24)
Hunt and Hess scale	2 (2, 3)
Hunt and Hess scale ≥ 3	72 (32)
Location at the time of SAH onset	
Work	22 (10)
Home	164 (73)
Others	38 (17)

Values are reported as mean ± SD, median (IQR), or number (percentage based on non-missing values). [†]Manual work includes construction, farming/forestry/fishing and related, installation and related, manufacture and production, transportation, and driver occupations. [‡]Coronary artery disease includes prior heart attack or angina. [§]Within the 3 months before SAH onset. [‖]Defined as body mass index ≥ 24 kg/m^2. [#]GCS - Glasgow Coma Scale, poor score ≤ 9 in range 3 (low) to 15 (high, normal).

the patients. Meanwhile, early complications (including rebleeding, hydrocephalus, seizures, and cardiopulmonary issues), vasospasm, and delayed cerebral ischemia (DCI) need to be recognized and treated promptly. IA patients require immediate neurosurgical or neuro-interventional consultation and can be treated with endovascular coiling or open surgical clipping[13]. The intervention type depends on the patient's complications, aneurysm anatomy, and surgical expertise[14]. According to the latest SAH recommendations, low-volume institutions should consider an early transfer of aneurysmal SAH patients to high-volume centers with experienced cerebrovascular surgeons, endovascular specialists, and comprehensive neurointensive care services[14].

According to our results, the clinical management of SAH in the northern urban Chinese population was characterized by a high use rate of the proven nimodipine therapy for the prevention of cerebral vascular spasms (CVS), and alternative medical therapies, including in-

Table II. Management and outcome of SAH patients in hospital.

Investigations/treatment/outcome at discharge	Total (N = 226)
Investigations	
Computerized tomography	218 (97)
Magnetic resonance imaging	27 (12)
Selective cerebral angiography	104 (46)
CT angiography or/and MR angiography	21 (9)
Site of the SAH patient's hospital management	
Intensive care unit	143 (65)
Length of intensive care unit stay(days)	8 (5,11)
Neurology ward with a stroke unit	93 (44)
Medical treatment	
Intravenous traditional Chinese medicine	89 (40)
Intravenous neuroprotectant	96 (43)
Intravenous haemodilution agents (eg mannitol)	209 (93)
Nimodipine	206 (92)
Intravenous	189 (85)
Oral	58 (27)
Intravenous tranexamic acid	165 (73)
Aneurysm intervention	
endovascular coiling	52 (26)
Neurosurgery clipping	10 (5)
Other	3(1)
Outcome at discharge	
Death in hospital	45 (20)
Experienced ≥ 1 in-hospital complication‡	89 (40)
Length of hospital stay, median (IQR)	24 (9, 34)
Modified Rankin Scale† at discharge	
0-2	140 (82)
3-5	31 (18)
Discharge destination for survivors	
Home	143 (84)
Alternate hospital	13 (8)
Other§	15 (9)

Values are reported as median (IQR) or number (percentage based on non-missing values). ‡Complications include pneumonia, ischaemic stroke, urinary tract infection, other sepsis, pulmonary embolus, coronary event, seizure, fall with injury, symptomatic cerebral vasospasm, symptomatic hydrocephalus, or any other clinically significant event that prolonged hospital stay. †Modified Rankin Scale, in range 0 (low, normal) to 5 (high, severe). §Includes family/friends' homes, nursing homes/institutions, and others.

travenous hemodilution agents (mannitol), neuroprotectants, and TCM in the acute phase. In addition, tranexamic acid (TXA) is often used in the acute period. In the northern urban Chinese population, the use rate of nimodipine (92%) was higher than elsewhere in China (63%)[15]. Nimodipine is the only approved medication after aneurysmal SAH[14,16]. It is suggested in all meta-analyses[17] that the preventive nimodipine is effective on SAH in reducing the probability of deficit and or death and decreasing the infarction rate on CT. However, every coin has two sides. Some studies[18] find that nimodipine treatment has certain negative effects on SAH patients, including hypotension, heparin-induced thrombocytopenia type 2, heart attack, self-limiting ventricular tachycardia, and dysrhythmias. Clinical outcomes improve significantly after continuous treatment and single nimodipine administration but deteriorate significantly with continuous nimodipine application[19]. Nimodipine administration is suggested[20] to be associated with intracerebral hemorrhage, heart rhythm abnormalities, infectious complications, and catheter thrombosis. Nevertheless, it is difficult to say whether one kind of nimodipine administration is better or safer than another. Although nimodipine can alleviate vasospasm in some cases, it also has systemic side effects that must be monitored to ensure appropriate dose adjustment or termination. In our study, patients receiving nimodipine treatment had a good prognosis with no serious complications. However, data on the nimodipine dosage, days of dosing, complications, and detailed comparisons were not collected in this study.

Alternative medical interventions such as intravenous neuroprotectants, hemodilution agents, and TCM were commonly used in our study. In general, mannitol can decrease excessive intracranial pressure (ICP) by reducing blood viscosity and increasing intravascular capacity. But hypertonic saline may be preferable to mannitol in lowering ICP in SAH cases[21]. However, neither hypertonic saline nor mannitol has been completely examined clinically. Mannitol or mannitol combined with hypertonic saline was more frequently used in this study, which achieved favorable patient outcomes. Nevertheless, this study did not examine the benefits of mannitol alone over mannitol combined with hypertonic saline. Although TCM (herbal/complementary therapies) has long been recognized with therapeutic benefits for a variety of illnesses in China, it is currently not included in the international guidelines for SAH management[22]. There has been evidence[23] supporting that some herbs, including *Salvia miltiorrhiza, Liguisticum chuanxiong*, *Ginkgo biloba*, *Pueraria lobata*, cow bezoar, and *Gynostemma pentaphyllum*, can effectively prevent and treat CVS. A study[24] has also reported that the traditional Chinese herbal combination, Qingnao Oral Liquid, may effectively relieve SAH-induced headaches. Herbal complexes like Angong Niuhuang Pills[25], Boyanghwano-tang[24], and Qingdao Oral Liquid[24] may effectively treat CVS or headaches post-SAH. In this study, *Salvia miltiorrhiza*, Xingnaojing Injection, *Liguisticum chuanxiong*, *Ginkgo biloba*, *Pueraria lobata*, and cow bezoar were utilized. Thus, herbal treatments may be novel possibilities for the prevention and treatment of CVS post-SAH, which may influence patient prognosis. A considerable number of clinical randomized controlled trials (RCTs) are still required to evaluate the efficacy of TCM in the treatment and prognosis of SAH.

TXA is not a standard of care. Instead, it is a strategy based on the case and local availability. In this study, TXA was used in the acute phase of aneurysmal SAH but not after aneurysm surgery, and for 3-7 days in patients without an aneurysm. TXA is demonstrated to lower the incidence of rebleeding after SAH, but it remains controversial concerning whether it can reduce mortality and improve clinical outcomes. As shown in a trial[26], TXA does not improve clinical outcomes, as evaluated by the modified Rankin score (mRS) at 6 months. In addition, it is recognized by the Neurocritical Care Society that, TXA and aminocaproic acid can decrease aneurysmal re-rupture, while the prolonged treatment can increase the risks of deep vein thrombosis, pulmonary embolism, and ischemic stroke[27]. According to a comprehensive review and meta-analysis[28] of RCTs, the routine administration of TXA after SAH is not recommended. However, the clinical outcomes and adverse occurrences among patients receiving TXA were not collected in this study. More high-quality studies are warranted in the future to evaluate the effect of TXA on patients with SAH.

Endovascular coiling occlusion of a ruptured IA was more common than neurosurgical clipping in this study. The disabled/dependent survivors achieved a good outcome, with the modified Rankin Scale scores of 0-2 at discharge. Endovascular coiling is a better surgical technique due to its fewer postoperative complications, good outcomes (MRS scores, 0-2), and rehabilitation[29]. For aneurysmal SAH patients, microsurgical clipping of the aneurysm is associated with considerably improved outcomes[30]. However, another Japanese study[31] reveals that surgical clipping is still being used to treat SAH. For patients with poor aneurysmal SAH, both coil embolization and microsurgical clipping are recommended[32]. Nevertheless, these two treatment techniques are not found to be superior among SAH patients, considering the therapy options available to each institution and the patient's contribution to maintaining the treatment outcomes.

Strengths and Limitations

The strengths of this clinical investigation include that it is a recent high-quality clinical and epidemiological study performed in the northern urban Chinese population, where research resources are scarce. However, certain limitations should be noted in this study. First, SAH management requires a multidisciplinary strategy, and the accuracy may be affected by hospital levels. Second, only the urban regions were investigated, which might limit the comprehensiveness of the result. There might be recollection bias in our medical history questionnaires, and our results might be associated with survivor bias because a tiny proportion of patients with seething severe diseases died before enrolment. These concerns are anticipated to have a minor impact on the outcomes due to a good correlation between self-reported medical history and medical records. In addition, any assessment of current management may benefit those who survive the first few hours after SAH onset.

Conclusions

Our findings on the management of SAH in the northern urban Chinese population have shown that nimodipine is an effective medical therapy with a high rate of use. There is also a high utilization rate of alternative medical interventions. In addition, endovascular coiling occlusion is more common than neurosurgical clipping. The regionally traditional therapy may be the key factor for the difference in the treatment of SAH between northern and southern China. Nevertheless, it is essential to comprehensively evaluate the treatments for SAH to improve outcomes from the devastating disease in a northern urban Chinese population.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

The authors declare that the patients included in the study signed informed consent forms to use their medical information in the studies.

Ethics Approval

The study protocol was approved by the Ethics Committees of the University of Sydney and Baotou Central Hospital.

Authors' Contribution

J.F. Zhang designed the study, advised on the interpretation and presentation of results, and participated in the critical revision of the manuscript. N.Y. Ma contributed to the design of the study, prepared and analyzed the data, interpreted the results, and drafted the manuscript. L. Lv and L. Zhang participated in the acquisition of data. W.S. Zhang participated in the critical revision of the manuscript. G.J. Cheng and H.M. Li advised on methods of data analysis, presentation of results, and critical revision of the manuscript. All authors read and approved the manuscript.

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