Medical and Research Publications
International Open Access

Research Article **Journal of MAR Neurology (Volume 3 Issue 2)**

Delayed Cerebral Ischaemia and Hyponatremia Following Aneurysmal Subarachnoid Hemorrhage in an Indian Subset.

Kanishk Parmar*, MBBS, DNB Neurosurgery, Srivatsan Thirumalai Vasu[1], MBBS, DNB Neurosurgery, Harish Srinivasan[2], MBBS, DNB Neurosurgery, Rahul Srinivasan[3], MBBS, DNB Neurosurgery, Chandan H Anandegowda[4], MBBS, DNB Neurosurgery, Vishnu P S[5], MBBS, DNB Neurosurgery, Lakshay Raheja[6], MBBS, DNB Neurosurgery, Mohammed Mansoor T[7], MBBS, DNB Neurosurgery, Tulsi Thampan[8], MBBS, DNB Neurosurgery

1,2,3,4,5,6,7,8. Department of Neurosurgery, Medical Trust Hospital, Pallimukku, M.G Road, Kochi, Kerala, India-682016.

Corresponding Author: Kanishk Parmar, MBBS, DNB**,** Department of Neurosurgery, Paras Global Hospital, Darbhanga, India – 846003.

Received Date: July 10, 2021

Published date: August 01, 2021

Abstract

Introduction: Delayed cerebral ischemia (DCI) is one of the most feared complications associated with aneurysmal subarachnoid hemorrhage (SAH). It is a potentially treatable cause of mortality and morbidity. Hyponatremia is the most common metabolic abnormality associated with SAH. Predictive values of hyponatremia on clinical outcome and DCI has been a subject of various studies with mixed results. This study is being done to determine the association of hyponatremia with DCI and poor outcomes.

Methods: *We did a prospective observational study at a single center between January 2016 and February 2019. 50 patients with WFNS grades 1-4 were included in the study. Serum Sodium values were recorded from day 1 to 10 of hospitalization. Information regarding demographics, hypertension, diabetes, admission WFNS grades and DCI were obtained and analyzed. The outcome was assessed after 3 months using eGOS. P<0.05 was considered significant.*

Results: *30 out of 50 patients developed hyponatremia (60%) and 27 patients developed DCI (54%). Among the hyponatremia group, 21 had evidence of DCI (70%), whereas, among the normonatremic group, 6 had DCI (30%). The chi-square test showed a statistically significant difference (p = 0.005) in proportions of DCI between normonatremic and hyponatremic groups but couldn't elicit similar results for the outcome (p = 0.273). The study showed a statistically significant difference (p<0.001) in proportions of outcome between the DCI absent and DCI present group.*

Conclusion: *Our results suggest a possible role of hyponatremia in predicting DCI development and poor clinical outcome.*

Keywords: *Hyponatremia, Delayed cerebral ischemia, vasospasm, aneurysmal subarachnoid haemorrhage, outcome.*

Abbreviations

DCI: delayed cerebral ischemia

SAH: subarachnoid haemorrhage

WFNS: World Federation of Neurosurgeons

ICU: intensive care unit

CT: computed tomography

GCS: Glasgow coma scale

GOS: Glasgow outcome scale

Introduction

Subarachnoid haemorrhage (SAH) is the pathologic condition that exists when blood enters the subarachnoid space. The most common cause of SAH is a head injury, with saccular (berry) aneurysms being the cause of 85% of spontaneous SAHs (Go et al.). There are approximately 600,000 cases worldwide annually (Feigin et al.). In India, the prevalence of aneurysmal SAH ranges from 0.75% to 10.3% with a higher number of cases being diagnosed due to the increasing age of the population and improvements in imaging techniques (Koshy et al.). More rapid recognition and evidence-based treatment protocols have led to a decline in the worldwide case fatality rate ranging from 17% to 50%. However, the prehospital and 30-day mortality rates continue to remain high (15% and 35%, respectively) (Lovelock et al.; Nieuwkamp et al.). Despite a decline in the mortality rates, SAH continues to remain a highly morbid disease with survivors commonly left with a permanent disability, cognitive deficits, and mental health symptoms, resulting in a significant reduction in health-related quality of life, which has been reported to occur in 35% of patients 1 year after SAH (Tjahjadi et al.; Vergouwen et al.; Al-Khindi et al.).

Cerebral infarction from delayed cerebral ischemia (DCI) is the leading cause of morbidity in patients who survive the initial SAH and hence, one of the most feared neurologic complications after SAH. De facto, it is the reason for prolonged ICU stay to promptly identify and treat DCI (Foreman). Newer studies have led to changes in the classic teachings of the etiology of cerebral vasospasm and DCI. While vasospasm has been traditionally linked to the development of cerebral ischemia several days after SAH, emerging evidence reveals that DCI is part of a much more complicated post-SAH syndrome (de Oliveira Manoel et al.). As a result, increasingly, some experts believe that cerebral vasospasm is only an epiphenomenon and the biochemical and biophysical changes that lead to DCI occur as early as at SAH onset (Macdonald and Weir; Macdonald et al.) This fundamental change in the approach to delayed cerebral ischemia has been the result of the exploratory analysis done using the data from CONSCIOUS-1 and CONSCIOUS-2 trials (Macdonald et al.; Stiefel and Petzold).

Hyponatremia is the most common electrolyte disorder in SAH and occurs in 30-55% of cases as per the data of various studies. Its cause is presumed to be hypothalamic dysfunction secondary to SAH (Fraser and Stieg; Levine). Regardless of the cause of hyponatremia, it can worsen the patient's neurological condition after SAH and increase the risk of mortality and morbidity (Qureshi et al.). The predictive value of hyponatremia on clinical outcome and correlation between cerebral vasospasm and hyponatremia has been a subject of various studies which are all retrospective in nature (Chandy et al.; Hasan et al.; Wijdicks et al.; Zimmermann and Seifert; Zheng et al.). Moreover, the results have been inconsistent with the failure to yield a predictive association. DCI is now known to have multifactorial pathophysiology and the principal objective of this dissertation is to determine the role of hyponatremia in anticipating the onset of DCI and treating it emergently.

We have attempted to address the lacunae in current knowledge by doing a prospective study to investigate the predictive association of hyponatremia and DCI and poor outcomes in case of aneurysmal SAH. Predicting who will develop DCI has proven to be very difficult but is of great importance. Not only does such prediction have an impact on ICU stay, early identification and management, but also on resource management and early ICU discharge for low-grade, lower risk patients with SAH. It will also help us in comparing Indian data with world data to determine differences in the outcome if any.

2. Methods

2.1 Study design and patient selection

A prospective surveillance cohort design was implemented for this study. The study was conducted in Medical Trust Hospital, a tertiary care center in Kochi, India. All adult patients diagnosed with aSAH presenting within 72 hours with a World Federation of Neurosurgical Societies (WFNS) score of 1-4 between January 2016 to February 2019 were included in the study. Patients who had (1) a WFNS score of 5, (2) mortality within 10 days, (3) fusiform/mycotic/traumatic aneurysms, (4) CT confirmed radiographic cerebral vasospasm on admission, and (5) serious medical comorbidities were excluded. A sample size of 50 was calculated to be sufficient. The study was performed after obtaining approval from the institutional ethics board and the need for informed consent was waived given the observational nature of the study.

2.2 Treatment strategy

Patients were admitted to the ICU, and an individualized treatment strategy for the aneurysm (Clipping/coiling) was used. Postoperatively, regular clinical and laboratory, as well as radiological screening, was performed. Hyponatremia was managed according to the institution's standard ICU protocols which included: (1) prevention of fluid restriction, (2) maintenance of euvolemia, and (3) ensuring daily optimum fluid intake by monitoring serum and urine osmolality, urine sodium values and CVP. 3% Hypertonic saline was used to correct hyponatremia below 130 mmoL/L or if persisting for >2 days.

2.3 Definition and Diagnosis

An absolute serum sodium value less than 135mEq/L was considered as hyponatremia and its incidence was recorded over the first 10 days, consistent with the literature (Qureshi et al.; Chandy et al.; Hasan et al.)

DCI was defined as one (or more) new neurological deficit(s), decline of two or more points on the Glasgow coma scale (GCS), or new hypodensities on the CT scan not visible on the admission or postoperative scan, and not associated with initial haemorrhage, and intracerebral hematoma, placement of a ventricular catheter, metabolic disturbance, infection, or hypoxia. Cerebral ischemia was verified on a CT scan by an independent neuroradiologist.

2.4 Data collection

Patient demographic, clinical and laboratory data were recorded systematically. History of systemic hypertension (defined in this study as intake of antihypertensive medication for at least 3 months prior to aSAH), Diabetes mellitus and history of smoking and alcohol consumption were also recorded. After admission, sNa levels were checked and recorded every 24 hours. Hyponatremia and its incidence were recorded over the first 10 days. The outcome was studied using a Glasgow outcome evaluation questionnaire during follow-up OPD visits or via telephonic interview. The outcome was assessed at 3 months with an extended Glasgow outcome Scale (eGOS). Poor outcome was defined as score 1-4 on eGOS with the scores of 5-8 being the good outcome.

Data was collected using a predetermined proforma on handwritten sheets and was later fed onto Microsoft Excel Worksheets.

2.5 Statistical analysis

SPSS (Statistical Package for Social Sciences) Version 24.0 (IBM Corporation, Chicago, USA) was used for data analysis. Continuous data are reported as mean +/- SD. Nominal data are reported as numbers and percentages. The test was used for univariate analysis while the independent sample t-test was used to compare means of groups of continuous variables. Statistical significance was set at $p<0.05$.

3. Results

3.1 Patient demographics

The mean age of the study participants in the normonatremia group was 48.30 ± 8.82 and in hyponatremia, group was 54.03 ± 10.98 ($p=0.057$). There were 11 (55.0%) males and 9 females (45.0%) in normonatremia group and 21 (70.0%) males and 9 females (30.0%) in hyponatremia group ($p=0.279$).

As shown in Table 1, there was no statistically significant difference in the WFNS scores, position of an aneurysm in the circle of Willis, comorbidities or consumption of alcohol or smoking in the normonatremia and hyponatremia groups.

Table 1: Patient characteristics

Category	**Normonatremia**		**Hyponatremia**		**p-Value**
	N	**Percentage**	**N**	**Percentage**	
Systemic Hypertension					
Present	13	65	20	66.7	0.903
Absent	7	35	10	33.3	
Diabetes Mellitus					
Present	7	35	7	23.3	0.368
Absent	13	65	23	76.7	
Alcohol Consumption					
Present	7	35	7	23.3	0.368
Absent	13	65	23	76.7	
Smoking					
Present	9	45	8	26.7	0.18
Absent	11	55	22	73.3	
WFNS score					
Score 1	10	50	11	36.7	0.309
Score 2	6	30	6	20	
Score 3	1	5	1	3.3	
Score 4	3	15	12	40	
Position of aneurysm					
Anterior Circulation	18	90	26	86.7	0.722
Posterior Circulation	2	10	4	13.3	
Outcome					
Good Outcome	15	75	18	60	0.273
Poor Outcome	5	25	12	40	

3.2 Delayed Cerebral Ischemia

As shown in Table 2, systemic hypertension was the only co-morbidity that was significantly associated with DCI (p=0.012). Diabetes mellitus, Alcohol consumption and smoking were not noted to be significantly associated with DCI.

The outcome was poor among patients with DCI (p<0.001). Mean WFNS scores did not influence DCI, with the mean WFNS score of the study participants in the DCI absent group 1.39 ± 0.72 and in the DCI present group 2.92 ± 1.23. There was no statistical difference (p=0.226). Table 3 shows the association between sodium values and DCI. Hyponatremia was noted to be significantly associated with DCI (p=0.005).

Table 2: Factors associated with DCI

Category	**DCI present**		**DCI absent**		**p-Value**
	N	**Percentage**	**N**	**Percentage**	
Systemic Hypertension					
Present	22	81.5	11	47.8	**0.012**
Absent	5	18.5	12	52.2	
Diabetes Mellitus					
Present	8	29.6	6	29.1	0.781
Absent	19	70.4	17	73.9	
Position of aneurysm					
Anterior Circulation	25	92.6	19	82.6	0.279
Posterior Circulation	2	7.4	4	17.4	NS
Outcome					
Good Outcome	10	37	23	100	**<0.001**
Poor Outcome	17	63	0	0	

Table 3: DCI and sodium levels

DCI	Normonatremia		Hyponatremia		p-Value
	N	Percentage	N	Percentage	
Present	6	30	21	70	0.005
Absent	14	70	9	30	

Table 4: Factors associated with outcome

Category	Good outcome		Poor outcome		p-Value
	N	Percentage	N	Percentage	
Systemic Hypertension					
Present	17	51.5	16	94.1	0.004
Absent	16	48.5	1	5.9	
Diabetes Mellitus					
Present	8	24.2	6	35.3	0.41
Absent	25	75.8	11	64.7	
Alcohol Consumption					
Present	12	36.4	2	11.8	0.066
Absent	21	63.6	15	88.2	
Smoking					
Present	13	39.4	4	23.5	0.262
Absent	20	60.6	13	76.5	
Position of aneurysm					
Anterior Circulation	28	84.8	16	94.1	0.339
Posterior Circulation	5	15.2	1	5.9	

3.3 Outcomes

Overall, outcomes were poor for patients with DCI, although sodium levels per se were not significantly associated with outcome. Systemic hypertension was associated with a poor outcome (Table 4). Evaluation of the eGOS based outcome at 3 months follow-up revealed that DCI had a statistically significant impact on the functional outcome even at 3 months as seen in Table 5. The admission WFNS scoring was also noted to significantly affect the outcome as depicted in Table 6.

Table 5: 3 months outcome and its association with DCI

DCI Present		DCI Absent		t-Value	p-Value
N	Mean ± SD	N	Mean ± SD		
27	4.66 ± 2.14	23	7.69 ± 0.47	-6.618	<0.001

Table 6: Outcome and its association with WFNS scoring

Good outcome		Poor outcome		t-Value	p-Value
N	Mean ± SD	N	Mean ± SD		
33	1.84 ± 1.12	17	2.94 ± 1.29	-3.094	0.003

4. Discussion

This prospective study was done in the Department of Neurosurgery, Medical Trust Hospital, Kochi over a three year period in view of the existing controversies and lack of consensus on published literature on DCI vis-à-vis Zheng et al, Chandy et al, Qureshi et al, Hasan et al, Vrsajkov et al, and Vladimir et al. The principle aim of this dissertation was possible role of hyponatremia in the prediction of DCI and poor outcome. (Zheng et al.; Chandy et al.; Qureshi et al.; Hasan et al.; Vladimir et al.; Vrsajkov et al.).

In our study, 60% of all aneurysmal patients developed hyponatremia during the observed period which correlates with Zheng et al which had 62.9% patients with hyponatremia. Other studies have shown comparable results – Chandy et al 39%, Qureshi et al 30%, Hasan et al 34%, Vladimir et al 38%, and Vrsajkov et al 39%. Only Wartenberg et al have shown only 14% incidence of hyponatremia in

aneurysmal SAH probably because of a more stringent definition of hyponatremia i.e. <130 mmoL/L. (Chandy et al.; Qureshi et al.; Hasan et al.; Vrsajkov et al.; Zheng et al.)

Hyponatremia has shown statistical significance (p 0.005) in predicting DCI as more patients had DCI in this group compared to normonatremia group. This is similar to the results shown by Vladimir et al, Vrsajkov et al, Hasan et al (24% cases of hyponatremia had CVS), Chandy et al (54% cases of hyponatremia had CVS). On the contrary, Qureshi et al has not shown any association between hyponatremia and symptomatic vasospasm. Wartenberg et al also failed to show any statistically significant relationship between the two. (Vladimir et al.; Vrsajkov et al.; Hasan et al.; Qureshi et al.; Chandy et al.)

There was no statistically significant difference between normonatremic and hyponatremic groups when compared for outcome at 3 months. However, normonatremic group had more patients with good outcomes than the hyponatremic group (75% vs 60%). The small size of the study may have been the reason for this result. Uniform protocol for prompt management and reversal of hyponatremia may be another reason for the same. This shows that DCI if anticipated and treated properly can lead to possibly better outcomes. Zheng et al also failed to show any relation of poor outcome with hyponatremia. However, a subset of the study group (late onset hyponatremia) was shown to be associated with cerebral infarction. (Zheng et al.)

Occurrence of hyponatremia had no relation on comparison with age, gender, hypertension, diabetes mellitus, admission WFNS score, smoking or alcohol which has been in consensus with other similar studies. The mean WFNS score of the study participants in normonatremia group was 1.85 ± 1.08 and in hyponatremia, group was 2.46 ± 1.35 in our study. One exception has been Vrsajkov et al, 2012, which has shown an association of hyponatremia with a higher WFNS score on admission. Zheng et al have shown a strong correlation between high-grade SAH (WFNS 4,5) and hyponatremia but failed to show similar relation with the low-grade WFNS groups. (Vrsajkov et al.; Zheng et al.)

27 (54%) out of 50 patients in our study matched the definition of DCI. The mean eGOS score of the study participants in DCI absent group was higher than in DCI present group with a high statistical difference (<0.001) in the mean eGOS score between DCI absent and DCI present group in our results. On the contrary Qureshi et al, Hasan D et al failed to show any significant outcome. Our findings were similar to the findings of Chandy et al and Vladimir et al. (Vladimir et al.; Chandy et al.; Qureshi et al.; Hasan et al.)

We failed to show any correlation between DCI with age, gender, diabetes, alcohol, smoking, admission WFNS score, or aneurysm location. However, statistical significance was noted in relation to hypertension. Hypertensive patients were noted to have a higher number of DCI occurrences in our study. Similar findings were noted in the study done by Vladimir et al, 2005. Hypertension is often associated with impaired myogenic response and autoregulation of CBF. Genetic variants in genes

involved in the regulation of cerebrovascular function are linked to hypertension, stroke, and dementia. This impaired autoregulation may be the reason for such a result. (Vladimir et al.) Hypertension and higher WFNS scores have also shown a positive correlation with poor outcomes in our study. These findings are consistent with the findings of Vladimir et al's prospective study done in 2015. The outcome has shown no relation to age, gender, diabetes, alcohol, smoking, low serum sodium level or aneurysm location. (Vladimir et al.)

Aneurysm location has failed to show any statistically significant relation with DCI or poor outcome. Findings were noted to be consistent with a similar study done by Vrsajkov et al. (Vrsajkov et al.). Vrsajkov et al, Chandy et al, and Qureshi et al are all retrospective studies with no uniform treatment protocols during the period of hyponatremia and hence of limited statistical power. These studies also lack any input on sodium intake by the patient during the stay. Wartenberg et al used moderate hyponatremia as a parameter and excluded mild hyponatremia and hence had a smaller number of hyponatremia patients in the study design. (Vrsajkov et al.; Chandy et al.; Qureshi et al.).

5. Limitations

The various limitations of our study when compared to other seminal papers on the subject can be enumerated as following – 1. A relatively small number of patients due to incidence of SAH at our hospital and exclusion of WFNS grade 5 from our study 2. The severity of hyponatremia or rapid fluctuation in sodium levels was not considered for predicting DCI (cf. Chandy et al) 3. The temporal relation of hyponatremia and DCI and outcome was not measured i.e. no time bound effect could be obtained. 4. Duration of ICU and hospital stay was not considered which has prevented us from comparing the cost factor.

6. Conclusion

This study suggests a certain correlation between the presence of hyponatremia and the risk of developing DCI in patients with aneurysmal SAH. These results reveal a possible use of hyponatremia as a predictor of developing DCI and poor outcomes. If treatment for hyponatremia is started promptly, DCI can be reverted so as to prevent morbidity and mortality.

References

1.Al-Khindi, Timour, et al. "Cognitive and Functional Outcome after Aneurysmal Subarachnoid Hemorrhage." *Stroke*, vol. 41, no. 8, Stroke, Aug. 2010, doi:10.1161/STROKEAHA.110.581975.

2.Chandy, Dipak, et al. “Hyponatremia and Cerebrovascular Spasm in Aneurysmal Subarachnoid Hemorrhage.” *Neurology India*, vol. 54, no. 3, Medknow Publications and Media Pvt. Ltd, July 2006, pp. 273–75, doi:10.4103/0028-3886.27151.

3.de Oliveira Manoel, Airton Leonardo, et al. “The Critical Care Management of Poor-Grade Subarachnoid Haemorrhage.” *Critical Care*, vol. 20, no. 1, BioMed Central Ltd., 23 Jan. 2016, pp. 1–19, doi:10.1186/s13054-016-1193-9.

4.Feigin, Valery L., et al. “Worldwide Stroke Incidence and Early Case Fatality Reported in 56 Population-Based Studies: A Systematic Review.” *The Lancet Neurology*, vol. 8, no. 4, Lancet Neurol, Apr. 2009, pp. 355–69, doi:10.1016/S1474-4422(09)70025-0.

5.Foreman, Brandon. “The Pathophysiology of Delayed Cerebral Ischemia.” *Journal of Clinical Neurophysiology*, vol. 33, no. 3, Lippincott Williams and Wilkins, 1 June 2016, pp. 174–82, doi:10.1097/WNP.0000000000000273.

6.Fraser, Justin F., and Philip E. Stieg. “Hyponatremia in the Neurosurgical Patient: Epidemiology, Pathophysiology, Diagnosis, and Management.” *Neurosurgery*, vol. 59, no. 2, Neurosurgery, Aug. 2006, pp. 222–28, doi:10.1227/01.NEU.0000223440.35642.6E.

7.Go, Alan S., et al. “Heart Disease and Stroke Statistics - 2014 Update: A Report from the American Heart Association.” *Circulation*, vol. 129, no. 3, 21 Jan. 2014, doi:10.1161/01.cir.0000441139.02102.80.

8.Hasan, Djo, et al. “Hyponatremia Is Associated with Cerebral Ischemia in Patients with Aneurysmal Subarachnoid Hemorrhage.” *Annals of Neurology*, vol. 27, no. 1, Ann Neurol, 1990, pp. 106–08, doi:10.1002/ana.410270118.

9.Koshy, Linda, et al. “Risk Factors for Aneurysmal Subarachnoid Hemorrhage in an Indian Population.” *Cerebrovascular Diseases*, vol. 29, no. 3, Karger Publishers, Feb. 2010, pp. 268–74, doi:10.1159/000275501.

10.Levine, Joshua M. “Critical Care Management of Subarachnoid Hemorrhage.” *Current Treatment Options in Neurology*, vol. 11, no. 2, Curr Treat Options Neurol, 2009, pp. 126–36, doi:10.1007/s11940-009-0016-6.

11.Lovelock, C. E., et al. “Time Trends in Outcome of Subarachnoid Hemorrhage: Population-Based Study and Systematic Review.” *Neurology*, vol. 74, no. 19, Lippincott Williams and Wilkins, May 2010, pp. 1494–501, doi:10.1212/WNL.0b013e3181dd42b3.

12.Macdonald, R. Loch, et al. “Clazosentan, an Endothelin Receptor Antagonist, in Patients with Aneurysmal Subarachnoid Haemorrhage Undergoing Surgical Clipping: A Randomised, Double-Blind,

Placebo-Controlled Phase 3 Trial (CONSCIOUS-2)." *The Lancet Neurology*, vol. 10, no. 7, Lancet Neurol, July 2011, pp. 618–25, doi:10.1016/S1474-4422(11)70108-9.

13.Macdonald, R. Loch, and Bryce K. A. Weir. "A Review of Hemoglobin and the Pathogenesis of Cerebral Vasospasm." *Stroke*, vol. 22, no. 8, Stroke, 1991, pp. 971–82, doi:10.1161/01.STR.22.8.971.

14.Nieuwkamp, Dennis J., et al. "Changes in Case Fatality of Aneurysmal Subarachnoid Haemorrhage over Time, According to Age, Sex, and Region: A Meta-Analysis." *The Lancet Neurology*, vol. 8, no. 7, Lancet Neurol, July 2009, pp. 635–42, doi:10.1016/S1474-4422(09)70126-7.

15.Qureshi, Adnan I., et al. "Prognostic Significance of Hypernatremia and Hyponatremia among Patients with Aneurysmal Subarachnoid Hemorrhage." *Neurosurgery*, vol. 50, no. 4, Neurosurgery, Apr. 2002, pp. 749–56, doi:10.1097/00006123-200204000-00012.

16.Stiefel, Dorothea, and Axel Petzold. "H2O Coma." *Neurocritical Care*, vol. 6, no. 1, Neurocrit Care, Feb. 2007, pp. 67–71, doi:10.1385/NCC:6:1:67.

17.Tjahjadi, Martin, et al. "Health-Related Quality of Life after Spontaneous Subarachnoid Hemorrhage Measured in a Recent Patient Population." *World Neurosurgery*, vol. 79, no. 2, World Neurosurg, Feb. 2013, pp. 296–307, doi:10.1016/j.wneu.2012.10.009.

18.Vergouwen, Mervyn D. I., et al. "Definition of Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage as an Outcome Event in Clinical Trials and Observational Studies: Proposal of a Multidisciplinary Research Group." *Stroke; a Journal of Cerebral Circulation*, vol. 41, no. 10, Stroke, Oct. 2010, pp. 2391–95, doi:10.1161/STROKEAHA.110.589275.

19.Vladimir, Vrsajkov, et al. "Prognostic Significance of Hyponatremia Leukocytosis, Hypomagnesemia, and Fever after Aneurysmal Subarachnoid Hemorrhage." *Indian Journal of Neurosurgery*, vol. 04, no. 02, Georg Thieme Verlag KG, July 2015, pp. 069–73, doi:10.1055/s-0035-1558961.

20.Vrsajkov, Vladimir, et al. "Clinical and Predictive Significance of Hyponatremia after Aneurysmal Subarachnoid Hemorrhage." *Balkan Medical Journal*, vol. 29, no. 3, Galenos Publishing House, 2012, pp. 243–46, doi:10.5152/balkanmedj.2012.037.

21.Wijdicks, E. F. M., et al. "Hyponatremia and Cerebral Infarction in Patients with Ruptured Intracranial Aneurysms: Is Fluid Restriction Harmful?" *Annals of Neurology*, vol. 17, no. 2, Ann Neurol, 1985, pp. 137–40, doi:10.1002/ana.410170206.

22.Zheng, B., et al. "A Predictive Value of Hyponatremia for Poor Outcome and Cerebral Infarction in High-Grade Aneurysmal Subarachnoid Haemorrhage Patients." *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 82, no. 2, J Neurol Neurosurg Psychiatry, Feb. 2011, pp. 213–17, doi:10.1136/jnnp.2009.180349.

23.Zimmermann, Michael, and Volker Seifert. “Endothelin and Subarachnoid Hemorrhage: An Overview.” *Neurosurgery*, vol. 43, no. 4, Neurosurgery, Oct. 1998, pp. 863–75, doi:10.1097/00006123-199810000-00083.