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Research Article

Correlation of carbon dioxide and systolic velocity of the middle cerebral artery in patients with spontaneous subarachnoid hemorrhage of aneurysmal origin

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ABSTRACT

Background: Aneurysmal Subarachnid Hemorhage (aSAH) secondary to an aneurysm is the most common presentation of nontraumatic SAH. Worldwide, the incidence varies, affecting more frequently women with an average age of 55 years. One of its main complications is cerebral vasospasm.
Objective: The objective of this study was to evaluate the correlation between blood flow of the middle cerebral artery and arterial CO_2 levels in patients with aSAH, comparing those who presented vasospasm in relation to those who did not.
Material and methods: Observational, historical cohort study, including patients between 18 and 85 years old, diagnosed with Aneurysmal Subarachnoid Hemorrhage (aSAH) secondary to an aneurysm (aSAH) Spearman/Pearson correlation coefficient was used to determine the correlation between mean velocity flow (MVF) by transcranial doppler and levels CO_2 serum according to the analysis group (with or without vasospasm). A value <0.05 was determined for statistical significance.
Results: Between 2015 and 2019 a total of 54 patients diagnosed with aSAH were treated in our institution, our results indicate a positive correlation between the SVRMCA and SVLMCA with the presence of vasospasm (p value = <0.001). No correlation was observed between serum CO_2 levels and SVRMCA or SVLMCA, irrespective of the presence of vasospasm.
Conclusion: In patients with aneurysmal subarachnoid hemorrhage, serum CO_2 levels do not correlate with cerebral systolic velocities. Further studies are required to confirm this finding.

1. Introduction

Aneurysmal Subarachnoid Hemorrhage (aSAH) secondary to an aneurysm (aSAH) is the most common presentation of nontraumatic SAH [1]. Worldwide, the incidence varies between 7 and 13 per 100,000 people/year, affecting women more frequently, with an average age of 55 years [2]. According to the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (WHO MONICA), the mortality reaches a rate of 25–30% after 30 days the appearance of an aSAH [3]. The main complications of aSAH are hydrocephaly,

Abbreviations: aSAH, Aneurysmal Subarachnoid Hemorrhage; MVF, Mean Velocity Flow; MCA, Middle Cerebral Artery; CO2, Carbon Dioxide; SVRMCA, Mean Systolic Velocity of the Right Middle Cerebral Artery; SVLMCA, Mean Systolic Velocity of the Left Middle Cerebral Artery.

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rebleeding, and cerebral vasospasm [4]. The severity of the vasospasm and the mortality is directly related to the bleeding volume and the initial neurological state after the event, generating an increased risk of cerebral ischemia [5].

Early diagnosis of vasospasm is relevant for the prognosis of these patients. Cerebral arteriography is the gold standard to diagnose cerebral vasospasm. However, there are other useful diagnostic methods that are non-invasive and have low cost such as transcranial doppler [6–7]. This last one evaluates changes in the Mean Velocity Flow (MVF) that suggests vasospasm when the velocity raises having a high sensitivity for anterior circulation (53%), anterior communicating artery (93%) and middle cerebral artery (98%). The vasospasm level is measured by the MVF of the Middle Cerebral Artery (MCA) directly related to the percentage of arterial narrowing. This divides vasospasm in: 1. Mild (MVF >120 cm/s and <25% arterial narrowing); 2. Moderate between 120 and 200 cm/s (25%–50%); severe >200 cm/s (50%) [8]. Reports show the sudden increase of 50 cm/s/24 h as a strong predictor of symptomatic vasospasm [9].

Under normal physiological conditions, Carbon Dioxide (CO_2) has a reversible effect on cerebral blood flow [10]. Hypercapnia causes significant vasodilation of the cerebral arterial system by the effect of hydrogens on vascular smooth muscle [11]. According to Schmieder et al. [8], the reactivity to CO_2 in the cerebral vasculature is not altered, indicating that the brain's self-regulation mechanism was preserved. This demonstrates the importance of measuring CO_2 reactivity and evaluating its use as a possible additional management of vasospasm.

The goal of treatment is to prevent rebleeding and late ischemic neurological deficit [5]. Triple H therapy (hypervolemia, hypertension, and hemodilution) is considered as the first line of therapy when the vasospasm is already established and symptomatic, however, there are few studies on this topic [12]. Despite advances in the management of aSAH, vasospasm occurs in approximately 50% of cases and continues to be an important cause of morbidity and mortality [6].

Following current evidence regarding CO_2 levels in relation with vasospasm, the aim of this study is to evaluate the correlation between the variables blood flow of the middle cerebral artery and arterial CO_2 levels in patients with aSAH, comparing those who presented vasospasm and those who did not.

2. Methodology

2.1. Study design

Observational historical cohort study, patients who voluntarily accepted their participation were included in this study by signing an informed consent. The study was approved by an ethics committee.

2.2. Population studied

Patients admitted at the hospital with a diagnosis of aSAH between 2015 and 2019 were included. The inclusion criteria were: Patients between 18 and 85 years of age diagnosed with subarachnoid hemorrhage, Patients that had an available result of a diagnostic arteriography, and those with available results of transcranial doppler for 14 days as a follow-up examination. Patients who entered the hospital with extra-institutional management or who did not meet the inclusion criteria were excluded.

2.3. Systematization and data analysis

After the review of the patient's medical records the variables included in the analysis were age, gender, comorbidities, simple skull computed tomography with the Fisher classification, Hunt and Hess classification, acute complication of subarachnoid hemorrhage, mortality and treatment. Transcranial doppler data was taken for the systolic velocities of the right and left middle cerebral artery and arterial gases to measure serum levels of carbon dioxide.

Patients with aSAH underwent digital subtraction angiography to locate cerebral aneurysms and assess the number of aneurysms displayed. In patients who did not undergone the procedure (due to kidney failure, hemodynamic instability, or bacteremia), the aneurysm could not be located. Daily monitoring during 14 days of evaluating the cerebral hemodynamic behavior with transcranial doppler in order to measure the speed of blood flow in the middle cerebral artery was made in all patients. Furthermore, arterial blood gases were taken almost simultaneously to the transcranial doppler.

2.4. Statistical analysis

A sample of 54 patients was needed, this size calculation was made considering the value of the correlation coefficient between the values of the systolic velocity of the middle cerebral arteries and the CO_2 blood level that can oscillate around $r = 0.54$ [13], with a typical error of 0.5, significance level 5%, and a power of 98%; calculating a loss percentage of 10%.

Analysis of data on demographic variables and medical history was performed: age, gender, or previous pathologies, among others. The qualitative variables in absolute and relative frequencies, and the quantitative variables with averages, typical error, medians and interquartile ranges were described. The D'Agostino-Pearson test was applied to determine if the quantitative ones presented normal distribution or not. Bivariate analysis had as purpose obtaining possible factors that are more or less related to vasospasm. Crosses were performed for the qualitative variables with chi square and for the quantitative variables with Student's *T* test or with the Mann-Whitney *U* test. The Grubbs test was used to determine the presence of abnormal data.

The Spearman/Pearson correlation coefficient was used to determine the correlation between MVF variables by transcranial doppler, mean systolic velocity of the right cerebral artery (SVRMCA), mean systolic velocity of the left cerebral artery (SVLMCA) and levels CO_2 serum according to the analysis group (with or without vasospasm). A value <0.05 was determined for statistical significance. The software used was R version 3.4.2–2017.

3. Results

Between 2015 and 2019 a total of 54 patients diagnosed with aSAH were treated in our institution. Table 1 shows the demographic characteristics of the population 72.2% (n = 39) of the patients were female. The mean age according to gender corresponds to 61.6 years (D.S. ± 15.7) in females and 46.7 years (D.S. ± 22.5) in males >70% of the patients presented at least one comorbidity. Hunt and Hess scale of 1 was reported in 46% patients; the most frequent form of presentation was Fisher 4 (51.9%). Of the 54 patients, 52% (n = 28) died (Table 1). Aneurysms were more frequently located in the anterior communicating artery 26% (n = 14), middle cerebral artery 17% (n = 9), posterior communication artery 13% (n = 7), 9% could not be located (n = 5), anterior cerebral artery 7% (n = 4), others localizations 2% (n = 1).

The number of aneurysms (p = <0.001) and the hydrocephalus (p = <0.001) showed a significant correlation with the presence of vasospasm (Table 1). Despite a non-significant correlation, the need of surgery (42.6%) was associated with more cases of post-event vasospasm (11%) compared to patients who undergone embolization (8%) (Table 1). During their hospitalization, the patients had vasospasm, hydrocephalus and rebleeding. Vasospasm was more frequent, appearing in 22 patients, corresponding to 40.7% and 5 patients with vasospasm and hydrocephalus, corresponding to 9.3% (Fig.1).

Data obtained from the MVF by the transcranial doppler, a mean SVRMCA of 85.4 cm/s and a mean SVLMCA of 84.8 cm/s. We found a significant correlation between the presence of vasospasm and velocity variations, SVRMCA increased to 150.8 cm/s (SE ± 9.5) and the SVLMCA to 142.9 cm/s (SE ± 7.9) (p value <0.001). Mean CO_2 levels

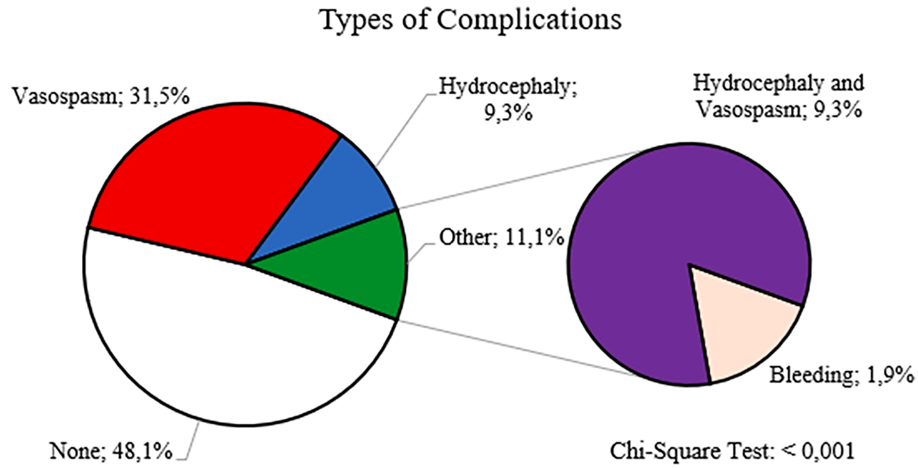

Fig. 1. Acute and subacute complications of patients with Aneurysmal Subarachnoid Hemorrhage of aneurysmal origin.

was 36.57 mg/dl (SE ± 0.5) with an increase up to 37.4 mg/dl (SE ± 0.8) in the group of patients with vasospasm (Table 2).

Table 3 shows a positive correlation between the SVRMCA and SVLMCA with the presence of vasospasm (p value = <0.001). On the other hand, no correlation was observed between serum CO_2 levels and SVRMCA or SVLMCA, irrespective of the presence of vasospasm (Table 4, Graphic 1 and Graphic 2).

4. Discussion

The poor prognosis of aSAH is directly related to the complications [14]. The mortality of the disease reaches 80% in multiple studies, this study showed a lower rate (52%) [15–17]. Higher scores in the severity scales are associated with unfavorable results like to patients with Hunt and Hess [18–20] and Fisher higher scores [21]; our results are consistent with this.

For example, in studies carried out in patients with MCA spasm induced by aSAH could cause cardiac ganglia degeneration based cardiac rhythm abnormalites and arrest [22], thermoregulation sensing cells degeneration based CSF abnormalites and cerebral hyperthermia [23] or cause carotid body degeneration based pH abnormalites and arrest [24]; all these factors can behave as predictors of unfavorable result or poor prognosis like the Hunt and Hess [18–20] and Fisher higher scores [21].

The demographic results of this study are consistent with previous reports [25–26], in relation to the risk factors for aSAH (female gender, arterial hypertension and location of the aneurysm in the posterior circulation [2,27,28], despite previous reports of posterior communicating artery as the most frequent cerebral aneurysm location, in this study, the anterior communicating artery (26%) was the most common location [29].

The incidence of complications as vasospasm depends on multiple variables. The treatment of choice in aSAH is usually reported without correlation with the presence of vasospasm, however, we found a significant difference in favor of the development of this complication in the group of patients that undergone clipping surgery, that could generate a hypothesis that has to be confirmed by more accurate studies [6,30].

The use of Transcranial Doppler is recommended to evaluate the presence of vasospasm [31]. As it was previously reported the increase in velocity of MCA is proportional to the severity of the vasospasm (specificity of 96% and PPV 87%) [32], our results, shows a significant correlation between vasospasm and variations in the flow velocities of the brain circulation (p value < 0.001).

The evidence regarding the effect of CO_2 variations on cerebral blood flow points to a brain self-regulation mechanism [10–11,33]. Animal models reports an association between post hemorrhagic microvasospasm and loss of reactivity to CO_2 in the first 3 h to 24 h after aSAH [34]. A study showed changes in the MVF of the MCA, after variations in $PaCO_2$ levels in patients under general anesthesia explained by an increase or decrease in cerebral vascular resistance and cerebral perfusion pressure [35–36]. Grune et al. [37], concluded that $PaCO_2$ not only causes changes in the vascular diameter at the level of the arterioles, but also minor changes in the diameter of the main trunk of the MCA [37].

In our study, serum CO_2 levels and arterial systolic velocities were not significant associated; however, we observed an increase in the systolic velocities of the middle cerebral arteries depending on the presence of vasospasm. More studies are needed to confirm these results and determine the increases in $PaCO_2$ as a viable option to treat vasospasm secondary to aSAH.

Limitations of this study are associated with the dependent operator analysis of the Transcranial Doppler and the small sample that could bias the results.

Few human studies have evaluated the CO_2 vasoreactivity in patients with aSAH. In this study, we found that systolic brain velocities were not modified by serum CO_2 levels. This allows us to hypothesize that the vascular response to CO_2 is different in patients with subarachnoid hemorrhage compared to the normal population, therefore, hypercapnia should not be considered as a therapeutic alternative.

5. Conclusion

In patients with Aneurysmal Subarachnoid Hemorrhage, serum CO_2 levels do not correlate with cerebral systolic velocities. Further studies are required to confirm these findings.

6. Ethics committee review/approval

This study was approved by the ethics committee.

CRediT authorship contribution statement

Juan Esteban Muñoz Montoya: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **José Nel Carreño Rodríguez:** Conceptualization, Methodology, Supervision, Project administration. **Gerardo Ardila Duarte:** Software, Validation, Formal analysis. **Miguel Ángel Maldonado Moran:** Visualization, Investigation, Resources. **Juan Carlos Luque Suarez:** Supervision, Data curation, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inat.2021.101402.

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