

The Relationship between Pulmonary Dysfunction and Age in Vasospasm Patients Receiving Triple H Therapy

Abstract

Background and Introduction: Triple H therapy is conventionally used to treat vasospasm following sub-arachnoid hemorrhage (SAH) but can sometimes have side effects. In order to investigate pulmonary complications in SAH patients and relationship with age we conducted the following study.

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Methods: The charts of 121 sub-arachnoid hemorrhage patients who underwent clipping or coiling of an aneurysm were retrospectively reviewed. The diagnosis of vasospasm was documented based on Doppler and angiographic findings. All patients with vasospasm received the standard Triple H therapy (hematocrit 33-38%, central venous pressure 10-12 mmHg, systolic blood pressure 160-200 mmHg). We studied intravenous intake, artificial ventilation, hypoxemia/pulmonary edema, postoperative fever, pneumonia and death rates as outcome variables.

Results: Sixty five patients developed vasospasm (15 mild, 23 moderate, 27 severe). These were significantly younger than non-vasospasm patients (51 years vs. 61 years, $p=0.004$). The average daily intravenous input was 1,730 cc in no-vasospasm patients, 2,123 cc in the mild vasospasm group, 2,399 cc in the moderate vasospasm group, and 3,040 cc in the severe vasospasm group. Younger patients with moderate to severe vasospasm received more fluids than older patients. Ten patients (8.3%) developed hypoxemia or pulmonary edema. No patient developed hypoxemia/pulmonary edema in the mild vasospasm group and the rates did not

show a trend and were not statistically different (7.1%, 0.0%, 13.0%, 11.1%, $p>0.05$) between vasospasm and non-vasospasm groups. Likewise, postoperative fever and pneumonia rates were not different between the vasospasm and non-vasospasm groups. Using the mean age as a threshold, pulmonary-related complications including death rates tended to be higher in the older group. The rates of postoperative ventilation (30.8% vs. 57.1%, $P<0.01$) and hypoxemia/pulmonary edema (3.1% vs. 14.3%, $P<0.05$) rates were statistically higher in the older group. Patients who developed hypoxemia/pulmonary edema in the vasospasm group tended to be younger than those who developed hypoxemia/pulmonary edema in the non-vasospasm group.

Conclusion: Younger patients are at a higher risk of developing vasospasm than older patients possibly referable to vessel elasticity and reactive sensitivity factors. Likewise, patients who developed hypoxemia/pulmonary edema in the vasospasm group were younger than in the non-vasospasm group possibly secondary to fluid overload from triple H therapy.

Keywords: Vasospasm; Triple H Therapy; Hypoxemia; Pulmonary Edema.

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Introduction

Cerebral vasospasm occurs angio-graphically in 70%-90% of sub-arachnoid hemorrhage (SAH) patients.¹ It is a critical condition that may lead to death or permanent neurological disability in 12-15% of patients.² Cerebral vasospasm is a complex multi-factorial process leading to a decrease in cerebral vessel diameter aiming at limiting the blood supply to the ruptured vessel and loss of auto-regulation.³ As a side effect, the brain parenchyma supplied by the narrowed arterial branches receives less amounts of blood perfusion and suffer ischemia.

While vasospasm can be viewed as a natural defense mechanism of the brain against hemorrhage expanding, the so-called "neurogenic pulmonary edema," sometimes associated with SAH, is not. In this paper we try to identify the relationship between cerebral vasospasm

Table 1: Table showing the demographic and clinical characteristics of the patient group with hypoxemia/pulmonary edema.

Age	Average Age	Gender	Race	BMI	Comorbidities	Vasospasm	Treatment of Respiratory Distress	Infection	Live/Dead
59	57.7	M	Caucasian	42	DM, HTN	Severe	Ventilator (hypoxia and pulmonary edema)	Sepsis (antibiotics)	Live
69		F	African-American	34	HTN	Severe	Ventilator (hypoxemia)	Sepsis-bacteremia (antibiotics)	Live
45		F	Caucasian	28		Severe	Ventilator (hypoxemia)		Live
51	53.5	F	Caucasian	25	DM, CHD, MI	Moderate	Ventilator (pulmonary edema)	Pneumonia, severe sepsis (antibiotics)	Live
56		F	Caucasian	33	HTN	Moderate	Ventilator (pulmonary edema)		Live
72	72.8	F	Caucasian	32	CHD	None	Ventilator (fluid overload,pulmonary edema, ARF)	Pneumonia, UTI, Klebsiella sepsis (antibiotics)	Live
67		F	African-American	26	DM	None	Ventilator, thoracocentesis, antibiotics		Live
79		M	Caucasian	27		None	Ventilator (hypoxemia and depressed mental status)	Pneumonia (antibiotics)	Live
67		F	Caucasian	22	CHD, COPD, Hypothyroidism, Dementia	None	BIPAP		Live
79		F	African-American	26	HTN	None	Ventilator (pulmonary problem)	Pneumonia (antibiotics)	Dead

and pulmonary edema with a third variable, age, which may help understand the mechanism of this complication in this category of patients.

Methods

The medical records of 121 patients [35% (n=42) male, 65% (n=79) female; 57% (n=69) Caucasian, 41% (n=49) African-American, and 2 % (n=3) mixed race; average age 54] who had sub-arachnoid hemorrhage as a result of a ruptured aneurysm and underwent clipping or coiling of aneurysm at the Medical Center of Central Georgia between 1998 and 2010 were retrospectively reviewed.

All patients with vasospasm received the Triple H therapy (hypertension, hyper-volemia, hemo-dilution), by combining intravenous medications and large volumes of intravenous fluids to elevate blood pressure to 160-200 mmHg, increase blood volume as reflected by central venous pressure to 10-12 mmHg, and decrease hematocrit to 33-38% aiming to drive blood flow through and around affected vessels by increasing pressure and blood volume and improving the rheology of blood flow in the cerebral micro-circulation.

The diagnosis of vasospasm was determined based on transcranial Doppler of the middle cerebral artery (MCA). Normal mean velocity for the MCA is within the range 62 ± 12 cm/sec; vasospasm corresponds to a mean velocity of 120 cm/sec; and velocities of 200 cm/sec or greater indicate severe spasm and indicate with 50% or greater narrowing on angiogram.⁴ We studied intravenous intake, artificial ventilation, hypoxemia measured by blood gases, pulmonary edema diagnosed symptomatically and by X-ray, postoperative fever (≥100° F), pneumonia and death rates as outcome variables. Due to close patho-physiology, we combined hypoxemia and pulmonary edema in one variable.

Results

Sixty five patients developed vasospasm (15 mild, 23 moderate, 27 severe). These were significantly younger than non-vasospasm patients (51 years vs. 61 years, p=0.004). The average daily intravenous input was 1,730 cc in no-vasospasm patients, 2,123 cc in the mild vasospasm group, 2,399 cc in the moderate vasospasm group, and 3,040 cc in the severe vasospasm group (Figure 1). Younger patients with moderate to severe vasospasm received

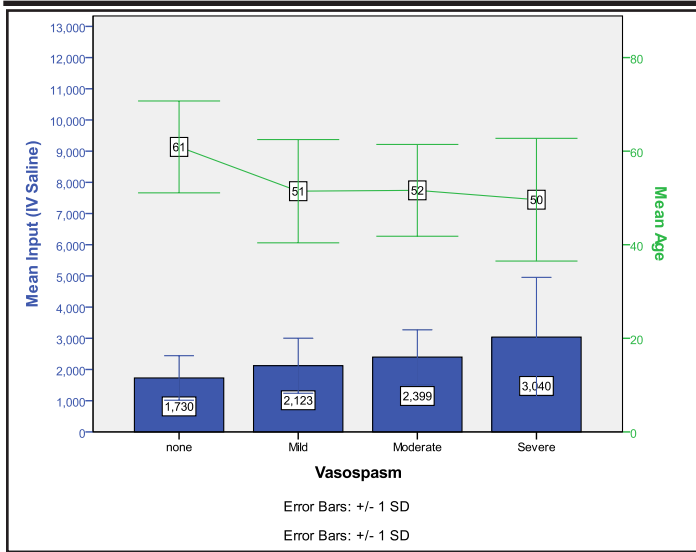


Figure 1: The average daily intravenous intake and age per vasospasm status.

more fluids than older patients (Figure 2).

Overall, 16 patients were initiated on artificial ventilation before surgical intervention on the ruptured aneurysm versus 52 patients who were on ventilation after surgery. There were significant differences in postoperative ventilation rates per vasospasm group (28.6%, 60.0%, 47.8%, 59.3%, $P < 0.05$, Figure 1). Not all patients were started on artificial ventilation because of pulmonary problems, instead, some for sedation purposes. Ten patients (8.3%) developed hypoxemia or pulmonary edema (Table 1). No patient developed hypoxemia/pulmonary edema in the mild vasospasm group and the rates did not show a trend and were not statistically different (7.1%, 0.0%, 13.0%, 11.1%, $p > 0.05$) between vasospasm and non-vasospasm groups (Figure 3). Likewise, postoperative fever and pneumonia rates were not different between the vasospasm and non-vasospasm groups.

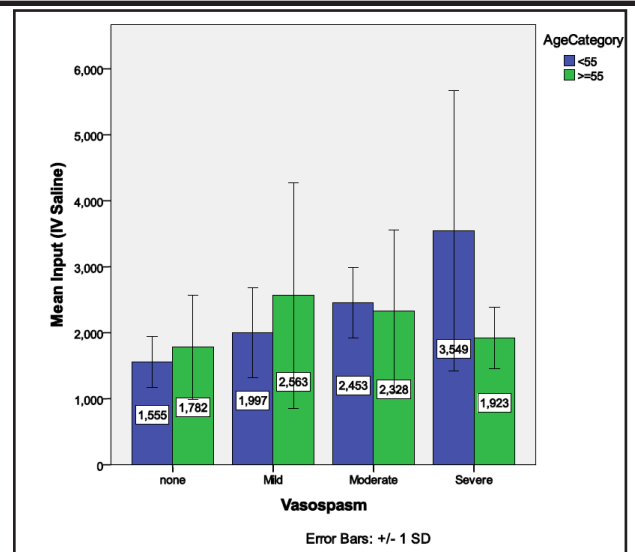


Figure 2: The average daily intravenous intake in younger and older patients with and without vasospasm.

Using the mean age as a threshold, pulmonary-related complications including death rates tended to be higher in the older group. The rates of postoperative ventilation (30.8% vs. 57.1%, $P < 0.01$) and hypoxemia/pulmonary edema (3.1% vs. 14.3%, $P < 0.05$) rates were statistically higher in the older group (Figure 4). Patients who developed hypoxemia/pulmonary edema in the vasospasm group tended to be younger than those who developed hypoxemia/pulmonary edema in the non-vasospasm group (Table 1).

Discussion

Triple H therapy is employed for the purpose of augmenting the blood supply to the affected sectors of the brain. Like any other therapy, it has side effects.^{2,5} Pulmonary edema is a serious complications that may blunt the efficacy of Triple H therapy and is thought to be the most common non-neurological cause

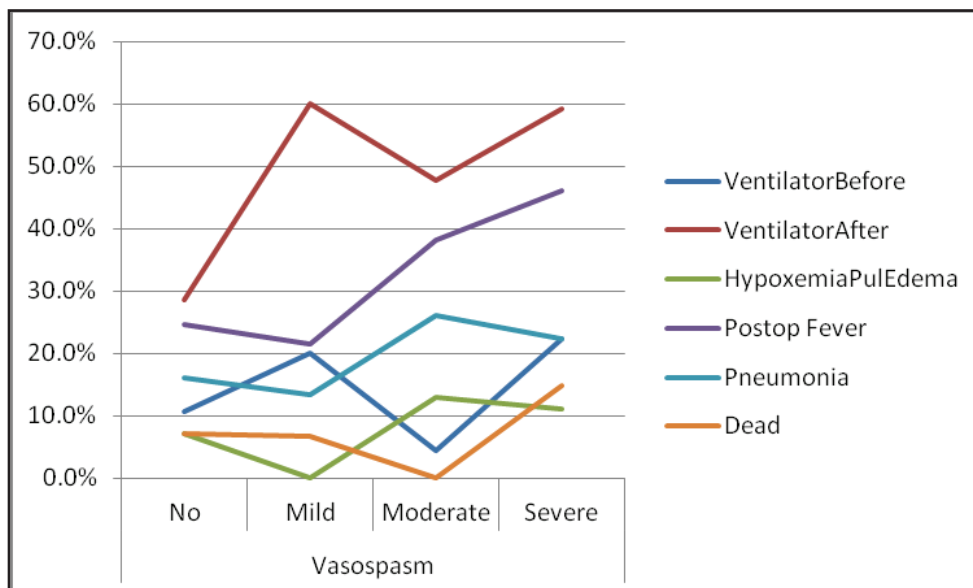


Figure 3: Pulmonary complication rates per vasospasm status..

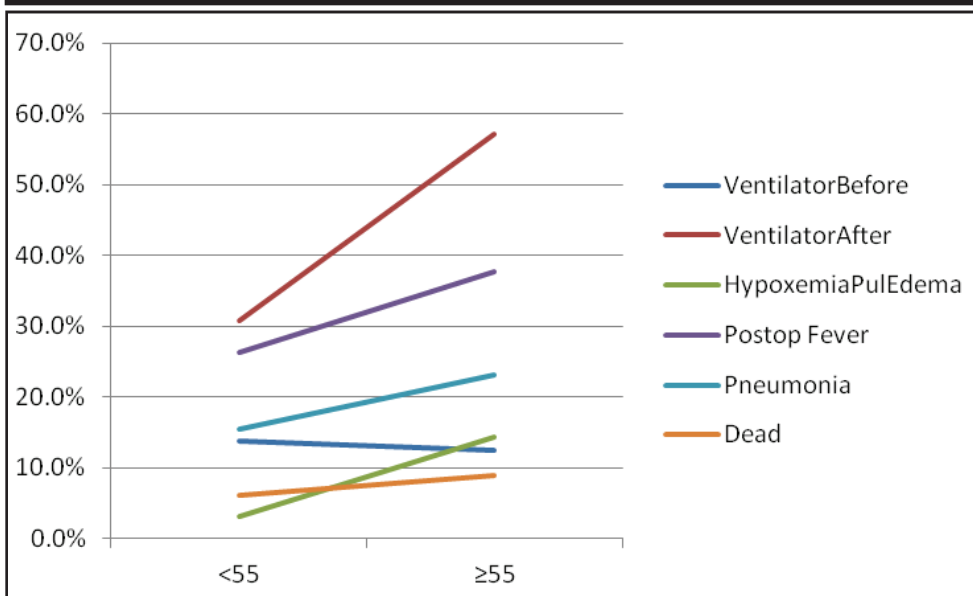


Figure 4: Pulmonary complication rates per age group.

of death in SAH patients.⁶ Studies show that many chemical agents that are released at the site of hemorrhage can cause vasoconstriction in cerebral arteries, including catecholamines, prostaglandins, serotonin, thrombin, various kinins, as well as various spasmogens induced by the blood clots formed at the hemorrhage site.⁵ However, the role of these agents in the development of pulmonary complications is not clear.

Treating patients with SAH receiving triple H therapy, it has been our experience that this treatment may result in deleterious effects. The literature testifies to the aggravating intracranial complications (cerebral edema, hemorrhagic infarction, posterior reversible leuko-encephalopathy) that may be caused by triple H therapy.^{7,8} The literature also mentions that patients who experience pulmonary complications after aneurysmal SAH have a higher incidence of symptomatic vasospasm and do worse than patients without pulmonary complications.⁹

Obviously, triple H therapy contributes to cardiopulmonary morbidity and mortality in SAH patients. Additionally, neurologic injury may result from hypoxia and the barometric damage from increased intra-thoracic pressure required to ventilate and oxygenate such patients. The current study shows a correlation between age and pulmonary complications. As expected, pulmonary vasculature of older patients tend to have lower capacitance and pulmonary venous pressures tend to reach higher levels due to decreased left ventricular compliance and preexisting cardiopulmonary disease. The finding that pulmonary edema/hypoxemia associated with vasospasm occurs in younger patients as well suggests that triple H therapy may be a significant contributing factor in its patho-mechanism. Neurogenic pulmonary edema, a poorly understood phenomenon, is thought to be primarily related to increases in pulmonary capillary hydrostatic pressure.¹⁰ In turn, triple H therapy, which increases circulatory volume and left heart filling pressures, may exaggerate this process.

On the other hand, our study shows that younger patients are at a

higher risk of developing vasospasm than older patients possibly referable to preserved vessel elasticity and reactive sensitivity. This is consistent with a previous study by Torbey et al., 2001, reporting a quadratic relationship between age and cerebral blood flow velocity ($P < 0.0001$); where older patients had a lower incidence of symptomatic vasospasm while vasospasm developed at lower cerebral blood flow velocity than in younger patients.¹¹ In our study, patients who developed hypoxemia or pulmonary edema in the vasospasm group were younger than those who developed this same condition in the non-vasospasm group, possibly secondary to fluid overload from triple H therapy. The capacity of the blood vasculature to tolerate larger volumes of fluid in younger patients allows them to receive higher amounts of fluids during the adaptation phase before pulmonary edema develops. Another explanation is that high blood pressure and low hematocrit (anemia) are common in older patients, a fact that helps minimize the amount of fluid needed to reach the obligatory thresholds of blood pressure and hematocrit, which in turn reduces the required fluid load in the pulmonary vasculature. Interestingly, decreasing hematocrit has minimal impact on blood flow in a constricted vessel according to latest studies.¹²

Since younger patients are at higher risk of developing vasospasm after SAH and being prescribed Triple H therapy, physicians focus on boosting the cerebral blood flow by increasing the cardiac outcome using medications or rarely by using the intra-aortic balloon pump counter-pulsation therapy¹³ rather than inducing hypertension and hyper-volemia by using pressors and infusing large amounts of fluids. This sounds reasonable since the vasospasm-susceptible group is the younger group while older patients are more vulnerable to fluid and electrolytes imbalance allowing a wider range of cardiac output manipulation in younger patients, which gives physicians the possibility to be more aggressive in treating younger patients than older patients. We ought to be careful however when administering large quantities of fluids as part of triple H therapy to young patients because this may add to the risk of neurogenic pulmonary edema and worsen the outcome.

More research is needed on pulmonary dysfunction rates among different age groups and on the impact of fluid overload precautions on neurological practice in sub-arachnoid hemorrhage patients. The question remains: shall we restrict Triple H therapy to patients with symptomatic vasospasm or change the target of therapy to less critical levels for elderly patients? The current study may support early moderate institution of endovascular treatment rather than late intensified treatment with Triple H therapy.

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