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Original Article

TOPICAL IRRIGATION OF PAPAVERINE DURING INTRACRANIAL ANEURYSM SURGERY IN PREVENTING CEREBRAL VASOSPASM

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Abstract:
Background: Derived from opium poppy (Papaver somniferous), papaverine is a non-analgesic opioid vasodilator employed in the treatment of vasospasm and impotency. Cerebral vasospasm, a major contributor to unfavorable outcomes in subarachnoid hemorrhage resulting from intracranial aneurysm rupture, prompted this investigation. The study aims to compare the incidence of ischemia in patients subjected to perioperative papaverine irrigation within the subarachnoid space during aneurysm surgery with those who did not receive preoperative papaverine treatment.
Materials and Methods: Conducted at Madras Medical College, Chennai, in 2022, this study involved 49 patients. Postoperatively, patients were closely monitored for cerebral ischemia, and evaluated through clinical and radiological indicators.
Results: Thirty-five patients with anterior communicating artery (ACOM) aneurysms and fourteen patients with middle cerebral artery (MCA) aneurysms were assessed for cerebral ischemia post-aneurysm clipping. The study compared outcomes between patients who underwent topical papaverine irrigation in the subarachnoid space and those who did not receive papaverine irrigation.
Conclusion: Papaverine irrigation during aneurysm surgery within the subarachnoid space effectively mitigates vasospasm and cerebral ischemia, consequently reducing morbidity and mortality associated with aneurysm surgery.

Keywords: aneurysm surgery, vasospasm, papaverine, cerebral ischemia

INTRODUCTION:

Intracranial aneurysms represent a critical medical condition often necessitating surgical intervention to prevent rupture and mitigate associated complications.[1] Cerebral vasospasm, a significant complication arising from subarachnoid hemorrhage secondary to intracranial aneurysm rupture, poses a considerable challenge in achieving successful surgical outcomes.[1,2] The role of vasodilators in preventing vasospasm during intracranial aneurysm surgery has been a subject of ongoing research. This study focuses on the topical irrigation of papaverine as a potential intervention to prevent cerebral vasospasm during intracranial aneurysm surgery, specifically conducted at a Tertiary Care Institute in Chennai.[3]

Background:

Papaverine, derived from the opium poppy (Papaver somniferous), is a non-analgesic opioid vasodilator that has demonstrated efficacy in the treatment of vasospasm and impotency.[2,3] Despite its established vasodilatory properties, the specific impact of topical papaverine irrigation during intracranial aneurysm surgery in preventing cerebral vasospasm remains an area of active investigation. Cerebral vasospasm significantly contributes to poor outcomes in patients with subarachnoid hemorrhage resulting from intracranial aneurysm rupture.[4] Addressing this issue is crucial to enhancing the overall success of aneurysm surgery and improving patient prognosis.

The rupture of intracranial arterial aneurysms is a prevalent cause of spontaneous subarachnoid haemorrhage, occurring at a rate of 6 to 8 cases per 100,000 in the population.[3] This condition carries a substantial mortality risk, with approximately 40 to 45% of affected individuals succumbing to it.[3] Notably, 10 to 15% of these fatalities occur within the initial 24 hours following spontaneous subarachnoid hemorrhage.[3,4] Vasospasm emerges as a significant concern, detected in 30 to 70% of cases within the first two weeks after the hemorrhage, constituting the primary cause of morbidity and mortality in this context.[5]

The etiology of vasospasm following subarachnoid hemorrhage involves endogenous spasmogens, such as oxyhemoglobin and endothelin, which inhibit Nitric oxide synthetase (NOS). Consequently, the reduction of endogenous vasodilators leads to the development of vasospasm. Surgical procedures involving the dissection and manipulation of blood vessels elevate the risk of vasospasm.[4,5,6]

While Triple H (H) therapy, incorporating hypertension, hypervolemia, and hemodilution, is the established treatment for vasospasm, it falls short of providing a definitive cure.[5,6] Intra-arterial vasodilators like papaverine present a potential avenue for treating cerebral vasospasm, but their use is limited by life-threatening side effects, including hemodynamic instability. Endovascular interventions, such as balloon catheterization and the local instillation of vasodilators at the vasospasm site, have been explored but are accompanied by inherent limitations.[3-5]

Research Gap:
While the literature acknowledges the potential benefits of papaverine in vasospasm management, there is a notable gap in the existing research regarding its specific application through topical irrigation during intracranial aneurysm surgery. The lack of comprehensive studies exploring the preventive effects of papaverine on cerebral vasospasm in the context of surgical procedures necessitates a focused investigation.[2, 4-5]

Rationale:
The rationale for this research stems from the need to address the existing gap in knowledge regarding the effectiveness of topical papaverine irrigation during intracranial aneurysm surgery. The potential benefits of vasodilation in preventing cerebral vasospasm and subsequent ischemic events justify a dedicated inquiry into the application of papaverine in this surgical setting.[4,5] By assessing the impact of topical papaverine irrigation, we aim to contribute valuable insights to the field of neurosurgery and enhance the armamentarium of interventions available for improving patient outcomes.

Novelty:
The novelty of this research lies in its specific focus on the application of topical papaverine irrigation during intracranial aneurysm surgery, conducted within the unique context of a Tertiary Care Institute in Chennai. This study seeks to provide novel insights into the preventive aspects of papaverine in the surgical setting, potentially paving the way for enhanced protocols in managing cerebral vasospasm during intracranial aneurysm surgery. The outcomes of this research may offer a valuable contribution to the evolving landscape of neurosurgical practices, with potential implications for improved patient care and outcomes.
This study endeavours to assess the efficacy of topical papaverine irrigation within the subarachnoid space during aneurysm surgery in reducing vasospasm and, consequently, mitigating cerebral ischemia. By focusing on the preoperative application of papaverine, this research aims to offer a safer and more targeted approach to addressing vasospasm, potentially contributing to improved outcomes in the management of spontaneous subarachnoid haemorrhage associated with intracranial aneurysm rupture.

OBJECTIVES OF THE RESEARCH:

1. To assess the Efficacy of Papaverine Irrigation:
   Evaluate the impact of topical papaverine irrigation during intracranial aneurysm surgery on the occurrence of cerebral vasospasm. Measure and compare the incidence of cerebral ischemia in patients who underwent papaverine irrigation in the subarachnoid space with those who did not receive this intervention.
2. To examine the Adverse Events and Safety Profile:
   Investigate the safety and tolerability of papaverine irrigation by documenting and analyzing adverse events associated with its application. Specifically, focus on monitoring occurrences of bradycardia and hypotension during and after papaverine irrigation to gauge the procedure's safety profile.

3. To characterize Demographic and Aneurysm-Specific Factors:
   Characterize the demographic features of the study population, including mean age and gender distribution. Additionally, it examines the distribution of aneurysm types, particularly focusing on the prevalence of anterior communicating artery (ACOM) and middle cerebral artery (MCA) aneurysms. Understanding these factors provides a foundation for contextualizing the study findings within specific patient demographics and aneurysm characteristics.

MATERIALS AND METHODS:

Study Design: Prospective study conducted at Madras Medical College, Institute of Neurosurgery
Duration: January to December 2022

Study Settings: Madras Medical College, Institute of Neurosurgery
Sample Size Estimated: A total of 49 participants were enrolled fulfilling the inclusion criteria set at the start of the study.

Sampling Technique: Utilized a simple random sampling method

Enrolment of Subjects: Criteria for Inclusion: Individuals experiencing spontaneous subarachnoid hemorrhage due to aneurysm rupture

Exclusion Criteria: Patients unwilling to undergo surgery, Patients with anesthesia complications preventing surgery and Patients not providing consent for participation in the study

Procedures Followed:
Thirty-five patients with anterior communicating (ACOM) aneurysm rupture and fourteen patients with middle cerebral artery (MCA) aneurysm rupture. Informed written consent was obtained from all participants. Aneurysm clipping was performed in both study groups. Following clipping and securing haemostasis, 40mg of papaverine, diluted in 20 cc of saline at 37°C, irrigated in the subarachnoid space around cerebral arteries, left to infiltrate for 10 to 15 minutes. The surgical site was washed with copious irrigation of normal saline. Hemodynamic parameters (pulse and blood pressure) monitored before, during, and after papaverine irrigation

Postoperative Monitoring: Participants were monitored for cerebral ischemia through clinical features and radiological findings as follows:

1. Clinical Features:

I. Neurological Examination: Regular assessments of neurological status, including motor function, sensory perception, and cognitive function.
II. Vital Signs: Continuous monitoring of vital signs such as heart rate, respiratory rate, and temperature.
III. Level of Consciousness: Frequent evaluation of the patient's level of consciousness using standardized scales like the Glasgow Coma Scale (GCS).

2. **Radiological Findings:**

I. Imaging Studies: Periodic imaging studies, such as computed tomography (CT) scans or magnetic resonance imaging (MRI), to assess the postoperative state of the cerebral vasculature, identify any signs of vasospasm, and detect potential complications.

II. Cerebral Angiography: In some cases, cerebral angiography may be employed to visualize the blood vessels and assess their patency.

3. **Hemodynamic Parameters:**

I. Blood Pressure Monitoring: Continuous monitoring of blood pressure to identify any fluctuations that could indicate changes in cerebral perfusion.

II. Pulse Monitoring: Regular assessment of pulse rate to detect alterations in cardiovascular function.

4. **Complications and Adverse Events:**

I. Hemodynamic Stability: Monitoring for any signs of hemodynamic instability during or after papaverine irrigation.

II. Infection Control: Observing for signs of infection at the surgical site, which may include redness, swelling, or increased temperature.

III. Adverse Reactions: Vigilance for any adverse reactions to papaverine, such as allergic responses or systemic complications.

5. **Fluid Balance:**

Hydration Status: Ensuring adequate hydration and monitoring fluid balance to prevent complications related to hypervolemia or dehydration.

6. **Papaverine Irrigation Specifics:**

I. Duration of Infiltration: Monitoring the duration for which papaverine is left to infiltrate in the subarachnoid space (10 to 15 minutes, as per the study protocol).

II. Temperature Control: Ensuring that the temperature of the papaverine solution and saline irrigation is maintained within specified ranges (37°C).

7. **Documentation:**

Record Keeping: Thorough documentation of all monitoring parameters, interventions, and observations in the patient's medical records.

Continuous and meticulous monitoring of these aspects is crucial for promptly identifying any signs of complications, assessing the efficacy of the intervention, and ensuring the overall well-being of the patient during the postoperative period.

RESULTS:

Table 1: Demographic Characteristics and Aneurysm Distribution

Characteristic	Result
Mean Age (years)	45 ± 5.5
Gender Distribution	Male: 26 (53%) Female: 23 (47%)
Aneurysm Type	ACOM: 35 (71.5%) MCA: 14 (28.5%)

Description: This table summarizes the demographic characteristics of the study participants and the distribution of aneurysm types. The mean age of the enrolled participants was 45 ± 5.5 years, with a slightly higher representation of males (53%) compared to females (47%). The majority of aneurysms were located in the anterior communicating artery (ACOM) accounting for 71.5%, while 28.5% were in the middle cerebral artery (MCA).

Interpretation: The demographic characteristics provide insights into the age and gender distribution of the study population, and the aneurysm-type distribution highlights the prevalence of ACOM aneurysms in this cohort.

Table 2: Papaverine Irrigation and Adverse Events

Characteristic	Papaverine Irrigation Group	No Papaverine Irrigation Group
Number of Patients	30	29
Adverse Events	Bradycardia: 2 Hypotension: 5	-

Description: This table outlines the number of patients who underwent papaverine irrigation during the study and details the adverse events observed in the papaverine irrigation group. Two patients in the papaverine irrigation group experienced bradycardia, and five patients developed hypotension.

Interpretation: The table provides a clear overview of the utilization of papaverine irrigation in the study and highlights the associated adverse events. Monitoring and managing these adverse events are crucial considerations when implementing papaverine irrigation in clinical practice.

Table 3: Incidence of Cerebral Ischemia

Characteristic	Papaverine Irrigation Group	No Papaverine Irrigation Group
Number of Patients	7	12
Percentage	23%	41%

Description: This table presents the incidence of cerebral ischemia in both the papaverine irrigation and no papaverine irrigation groups. Seven patients (23%) in the papaverine irrigation group and twelve patients (41%) in the no papaverine irrigation group experienced cerebral ischemia due to vasospasm.

Interpretation: The table underscores the varying incidence of cerebral ischemia in the two groups, suggesting a potential protective effect of papaverine irrigation in reducing the occurrence of cerebral ischemia associated with vasospasm during the postoperative period. Further analysis and consideration of the clinical implications are warranted.
These tables provide a detailed breakdown of the descriptive statistics, including mean age, gender distribution, aneurysm types, papaverine irrigation details, adverse events associated with papaverine, and the incidence of cerebral ischemia in both the papaverine irrigation and no papaverine irrigation groups.

Table 4: Summary Statistics

Characteristic	Result
Mean Age	45 ± 5.5 years
Gender Distribution	Male: 26 (53%) Female: 23 (47%)
Aneurysm Type	ACOM (Anterior Communicating Artery): 35 patients (71.5%) MCA (Middle Cerebral Artery): 14 patients (28.5%)
Papaverine Irrigation	Done in 30 patients; Not done in 29 patients
Adverse Events (Papaverine Irrigation Group)	Bradycardia: 2 patients Hypotension: 5 patients
Cerebral Ischemia Incidence	Papaverine Irrigation Group: 7 patients (23%) No Papaverine Irrigation Group: 12 patients (41%)

This tabular representation summarizes the key findings from the research, providing a clear overview of the demographic characteristics, distribution of aneurysm types, papaverine irrigation details, adverse events, and the incidence of cerebral ischemia in both groups.

DISCUSSION:

Cerebral vasospasm is characterized by the radiological attenuation of cerebral vessels, a condition that results in decreased cerebral perfusion, ultimately leading to cerebral ischemia. This ischemia can manifest as either symptomatic or asymptomatic, with transient ischemia or complete infarction being potential outcomes. [2,3] Clinical symptoms vary based on the specific vessels and cerebral regions affected. The management of vasospasm in subarachnoid hemorrhage remains challenging, with limited effective interventions available.[2,3]

Papaverine, an opium alkaloid, acts directly on the smooth muscle cells of cerebral vessels, inducing vasodilation. Its mechanism involves the inhibition of cyclic adenosine monophosphate and cyclic guanosine 3 and 5 monophosphate, leading to increased Nitric oxide and subsequent vasodilation.[2,3] While previous studies have primarily focused on the intra-arterial administration of papaverine, our investigation uniquely explores the effects of intracisternal papaverine use on vascular tone. Unlike intra-arterial injection, intracisternal papaverine irrigation avoids the need for neuroradiological intervention and minimizes hemodynamic side effects. [2,5]

Intra-arterial papaverine injection has been associated with various complications, including mydriasis, confusion, convulsions, reversible depression of the brainstem, increased intracranial pressure, hypotension, bradycardia, and thrombocytopenia. Similarly, intracisternal injection of papaverine may result in mydriasis, seventh nerve palsy, and malignant hyperthermia. [2,3]

Our study focuses on the novel approach of irrigating the subarachnoid space with papaverine during aneurysm surgery. In this intervention, the incidence of cerebral ischemia was 23%, significantly lower than the 41% observed in patients who did not undergo papaverine irrigation. This suggests a potential protective effect of papaverine irrigation against the development of cerebral ischemia in the context of aneurysm surgery. [2,6,7] The avoidance of intravascular administration reduces the likelihood of systemic complications associated with papaverine, emphasizing the potential clinical significance of this approach.

CONCLUSIONS:

1. Effect of Papaverine Irrigation on Cerebral Vasospasm:
The utilization of papaverine irrigation during aneurysm surgery demonstrated a significant impact on the incidence of cerebral vasospasm. A lower occurrence of cerebral ischemia was observed in the papaverine irrigation group (23%) compared to the group without papaverine irrigation (41%). This suggests that topical papaverine application in the subarachnoid space may contribute to a reduction in vasospasm-associated complications.

2. Demographic and Aneurysm Characteristics:
The study population exhibited a mean age of 45 ± 5.5 years, with a slightly higher representation of males. The majority of aneurysms were located in the anterior communicating artery (ACOM). These demographic and aneurysm distribution findings provide a contextual understanding of the characteristics of the enrolled participants.

3. Adverse Events Associated with Papaverine Irrigation:
The adverse events associated with papaverine irrigation included bradycardia in 2 patients and hypotension in 5 patients. While these adverse events should be acknowledged, the overall incidence was relatively low, suggesting that papaverine irrigation is generally well-tolerated.

4.Clinical Implications:
The study's findings support the hypothesis that topical irrigation of papaverine in the subarachnoid space during aneurysm surgery contributes to a significant reduction in cerebral vasospasm and associated ischemic events. This has potential implications for improving postoperative outcomes and reducing morbidity in patients undergoing surgical intervention for intracranial aneurysms.

5. Considerations for Future Research:
Further research is warranted to explore the long-term effects of papaverine irrigation, potential variations in outcomes based on different aneurysm locations, and the generalizability of these

findings to a broader population. Additionally, ongoing monitoring of adverse events and refinement of the technique may enhance the safety profile of papaverine irrigation.

In summary, the study provides valuable insights into the effectiveness and safety of topical papaverine irrigation during intracranial aneurysm surgery, emphasizing its potential as a preventive measure against cerebral vasospasm and ischemia. These conclusions contribute to the evolving landscape of neurosurgical practices and may guide future research and clinical considerations in the management of subarachnoid hemorrhage due to aneurysm rupture.

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Figures:

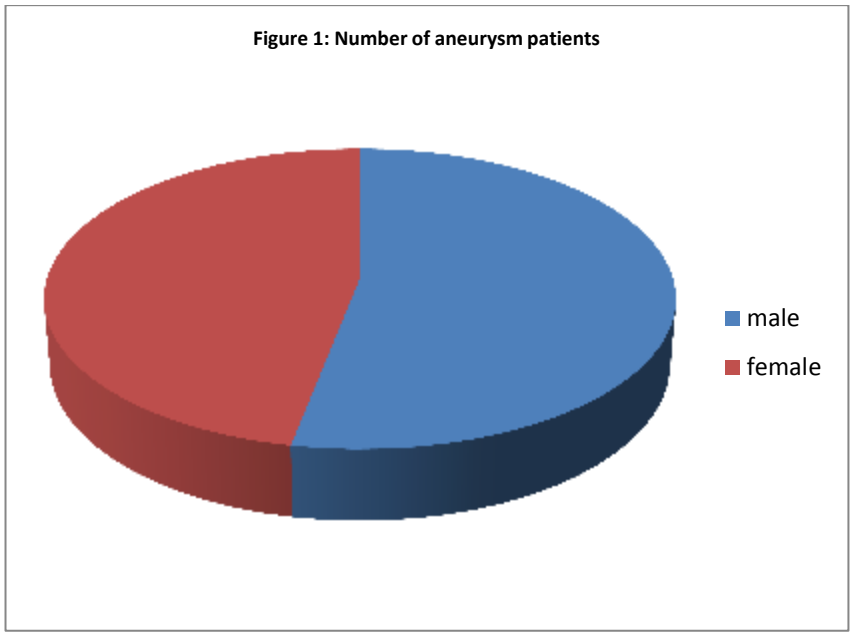
Figure 1: Number of aneurysm patients
male
female

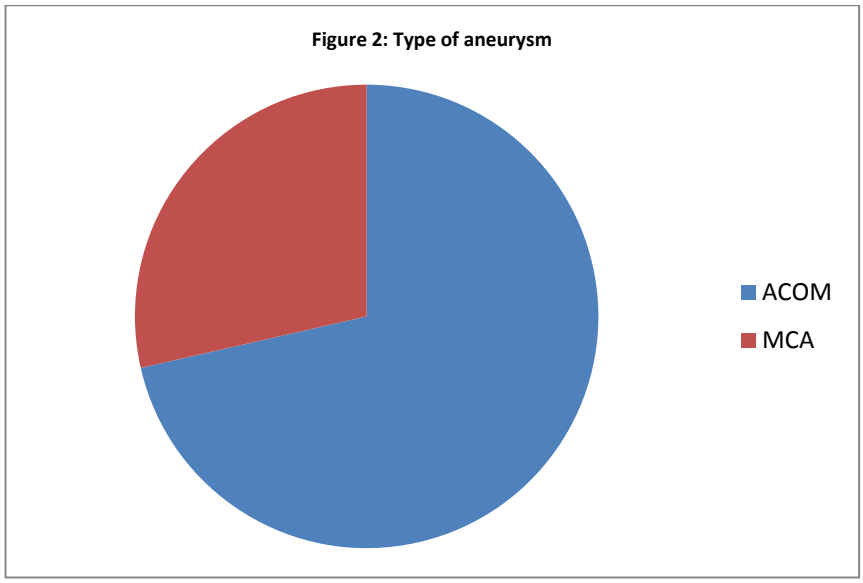
Figure 2: Type of aneurysm
ACOM
MCA

Figure 3: Status of papaverine irrigation