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Intravenous Nimodipine in Initial Intensive Care Management of Vasospasm in Aneurysmal Subarachnoid Haemorrhage – A Review

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Research Article

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Abstract

Background: As known to every Neuroscientist the spontaneous subarachnoid haemorrhage is a medical condition in which bleeding occurs in subarachnoid space due to cerebrovascular disease most commonly due ruptured aneurysms. Nimodipine is a calcium channel antagonist used to treat vasospasm. When compared to oral, intravenous nimodipine shows better neurological outcome with low dose, less frequency of administration and less fluctuations of blood pressure in between doses (as in oral) due to availability of continuous infusion . Titrated dose Intra venous nimodipine is useful in the initial Intensive Care management of Subarachnoid haemorrhage for Vasospasm with close monitoring of blood pressure.

Objective: To evaluate the clinical outcomes of intravenous Nimodipine in the management of acute ischemic vasospasm in subarachnoid hemorrhagic patients.

Material and methods: The study was a prospective and observational study conducted in all inpatients with SAH having acute ischemic vasospasm in the intensive care unit using IV Nimodipine admitted the department of Neurosurgery in AIMS during a period of 1yr.

Results: Evaluation of SAH occurrence in study patients (n=38) showed predominance of females (68.4%) and majority with hypertension (57.9%) as the common comorbid condition. The chance of developing SAH was high in patients who did not practice any form of exercise (60.5%). None of the patients had occurrence of adverse drug reactions while administering IV nimodipine other than hypotension which was corrected with inotropic support with close blood pressure monitoring. Out of the subjects enrolled, 37 patients showed improvement clinically and resolution of ischemic changes in CT scan . Majority of patients experienced cerebral edema. Using pair t test, it was found that the difference between the Glasgow Coma Score pre and follow up post treatment score were mild. Using pair t test, it was found that the difference between the mRS pre and follow up post treatment score were significant.

Conclusion: Introduction of IV Nimodipine to the treatment strategy of SAH showed significant improvement in the clinical and radiological outcome.IV Nimodipine showed benefit in treating the condition without any life-threatening adverse events other than correctable hypotension. A significant decrease in the mRS score in majority of patients after treatment indicates the improvement in the quality of life of SAH patients. Pre and Post neurological status strengthens the evidence of improvement in our study subjects.

Key Message

An evidence regarding the beneficial use of IV nimodipine in the management strategy of vasospasm in SAH.

Introduction

Aneurysmal subarachnoid haemorrhage is a health burden with a greater fatality and permanent disability rates. [1] It is a preventable and treatable disease to great extend. [2] Globally, the estimated incidence of SAH is 9/100,000 persons/y with the regional variation. Early diagnosis and management of the aneurysm can prevent re-rupturing of aneurysm and further complications associated with SAH. [3] Risk factors for development of SAH include current or previous cigarette smoking, coffee drinking, and hypertension, excessive alcohol, non-white ethnicity, female gender, family history of hemorrhagic strokes in first degree relatives, cocaine abuse and elder people (>60 years), estrogen compounds, hypercholesterolemia, and diabetes mellitus are major risk factors for aneurysmal SAH.[4,5,6,7] Symptoms associated with SAH are a stiff neck, photophobia, convulsions or loss of consciousness, double or blurred vision, slurred speech, severe headache termed as thunderclap headache and weakness on one side of the body.

Complications of SAH include seizures, hydrocephalus, rebleeding, delayed cerebral ischemia associated with cerebral vasospasm. [8] There are mainly two approaches to prevent this condition such as surgical clipping of the neck of the aneurysm or blocking the aneurysm from inside by endovascular coiling. [9] One of the major cause of death and permanent disability in patients having aneurysmal subarachnoid haemorrhage is post hemorrhagic cerebral vasospasm (PHCV). Currently, the common medications for preventing and treating cerebral vasospasm were categorized into the following medications: calcium channel blocker (nimodipine, nicardipine and verapamil), fasudil, magnesium, statins, hormones (Estrogen, Erythropoietin), phosphodiesterase inhibitor(Cilostazol, Papaverine, Milrinone), endothelin-1 antagonists, nitric oxide, heparin and fibrinolysis. Oral Nimodipine is recommended as prophylaxis whereas continuous IA nimodipine infusion recommended to deliver long term vasodilatory therapy.[10] Magnesium sulfate in combination with nimodipine can reduce the incidence of CVS and the incidence of secondary cerebral ischemia. [11] The area under the curve (AUC) values during parenteral nimodipine administration (median 149.3 ng-h/ml) were significantly higher than during oral administration on days 9 (median 92.1 ng-h/ml) and 12 (median 44.1 ng-h/ml). The AUC values during enteral administration were higher in patients who were on nimodipine orally than in those who received it by gavage. [12]

Nimodipine is the most widely and commonly used calcium channel blocker in the treatment of SAH. [13] Oral nimodipine administered 60 mg 4 hourly was observed to reduce cerebral infarction and improve outcomes following subarachnoid haemorrhage. [14] It was evidently proven that oral nimodipine improves the overall outcome. There are only few supporting studies stating the effectiveness of nimodipine when administered intravenously[22]Yuqian Li etal. Based on the present evidences, intravenous administration of calcium antagonists are rarely recommended for routine practice. Konstantin etal [23] studied comparison of Intravenous nimodipine with controls and found there is significant efficacy in the treatment of vasospasm.

Aim

To evaluate the clinical outcomes of IV Nimodipine in the management of acute ischemic vasospasm in subarachnoid haemorrhage patients.

Methods And Materials

A prospective and observational study was conducted in the department of Neurosurgery, Amrita Institute of Medical Science and Research Center (AIMS). A total of 38 patients were selected during the study period from September 2018 to March 2019.

Inclusion and exclusion criteria

The patients who met the following criteria were eligible to participate in the study: Subarachnoid haemorrhage, age below 80 years, patients in which aneurysm coiling and clipping has been done for the rupture, patients whose conditions were clinically and radiologically monitored.

Patient with known hypersensitivity to nimodipine; uncontrollable irritability; others factors that affect blood pressure; intra cerebral haemorrhage and other strokes; pregnancy, lactation and parturition; patients with cardiological disorders and those who did not come for follow ups.

The (Electronic Medicines Compendium followed in UK, Europe) [21] approved dosage of Intravenous preparation of Nimodipine 0.02% sterile solution in aqueous alcoholic solvent (10ml/50ml preparations available) was used in the intensive care immediate postoperative period till second week (maximum 14days) of date of haemorrhage then switched over to oral nimodipine or till clinical and neurological status becomes stable. The preparation is meant for Intravenous use only and different from oral preparations (as per FDA regulations oral preparations should not be used for injections). The dosage method as recommended was 15microgram/kg/hour of diluted nimodipine solution on staring treatment and increased up to 30microgram / kg/hour if the neurological status deterioration is seen. The infusion is done through central venous catheter with close Blood pressure monitoring in intensive care unit. All cases which do not improve with IV infusion are taken for endovascular treatment of Vasospasm such as chemical or balloon angioplasty with judicious approved dosage only and maintained with IV infusion of nimodipine post intervention. All cases are of high grade subarachnoid haemorrhage WFNS grade 3 or above. Initially subject's Clinical assessment included blood pressure (BP) and heart rate (HR) evaluation, Neurological examination, Transcranial Doppler velocities and Radiological assessment - CT scan were done. The subjects were followed up throughout the hospital stay and after 2 months using clinical, Neurological, Transcranial Doppler velocities and radiological examination .The information regarding adverse reactions are obtained by direct interview with patients or intensive care staff or from hospital information system. No ADRs were observed in the study subjects other than correctable hypotension in the prescribed doseof Nimodipine hence Naranjo ADR probability scale was not performed. During the follow up, patient's quality of Life was assessed using mRS scale. Improvement in neurological deficit and functional disability was assessed by Glasgow coma scale, mRS scale and modified Fischer Scale.

Ethical Committee approval was obtained from authorities for this study

Statistical Analysis

The information recorded on the data collection forms were uploaded in an excel sheet and data was analyzed using IBM SPSS 20.0 (SPSS Inc, Chicago, USA). For all the continuous variables, the results are either given in Mean ± SD, and for categorical variables as percentage. To test the statistical significance of differences in mean values from baseline to follow-up period, paired t-test were applied for parametric data. A p-value of <0.05 was considered significant.

Results

A total of 38 cases were selected for the study. The median age of patients in the study was 50 years (range 21-80) and the mean age was found to be 56.013± 12.71. Majority of the cases were females (68.4%). Most patients in this study had a past medical history of hypertension (57.9%) and diabetes mellitus (23.7%), followed by hypercholesterolemia (7.9%), hypothyroidism (7.9%) and family history (28.9%). The exercise habit prior to the disease condition showed that those who did not practice any form of exercise (60.5%) was high.

The patient underwent both the described procedures (Surgical Clipping and Coling) for management of ruptured aneurysm are studied the numbers are - 33 (86.84%) patients underwent endovascular coiling and only 5 (13.15%) of them underwent surgical clipping procedure. IV Nimodipine was judiciously used under close monitoring of blood pressure with recommended dosage, Inotropioc support was added in cases with patient with hypotension below acceptable limit of cerebral perfusion.

Assessment of clinical neurological status and CT scan changes of cerebral ischemia was carefully monitored in all patients.

There was significant difference in systolic blood pressure (0.001) and no markable difference in HR (0.060) between pre- and post-treatment. (Table No. 1)

Clinical assessment, Neurological assessment and Improvement of Transcranial Doppler velocities showed improvement or no deterioration in all cases ; Radiological assessment of pre and post treatment using CT scan showed resolution of existing ischemic changes in 37 patients . The mean duration for resolving SAH was obtained as 24.8 days. Quality of life assessment was based on Glasgow coma scale (GCS) and modified Rankin scale (mRs). There was significant difference between mRS pre- and post-treatment score (Table No. 2) while no significance between the GCS pre- and post-treatment score was observed. (Table No. 3)

Various factors influencing outcome was evaluated using mRS scale as the main indicator for the prediction of outcome in SAH patients. A score of 3 or above is considered as poor outcome and a score <3 is considered as good outcome. From the results we obtained, hypertension and diabetes mellitus had the significant association with the outcome.

Discussion

Studies on patients having acute vasospasm in SAH focused on the long term outcomes rather than the short term ones.[15] They evaluated recurrence of haemorrhage or vasospasm and functional disability of the patients after a period of 6 months whereas in our study we evaluated the patient's improvement based on clinical, neurological and radiological examinations and quality of life using mRS during a follow up of 2 months. The prognosis of SAH depends upon concomitant risk factors and in the hospital management.

Smokers, Autoimmune disease background higher Fischer grade SAH are more prone to develop vasospasm compared to other groups without these (20). The incidence of vasospasm differs in different population. Mechanism of vasospasm is multifactorial and beyond the scope of this study. Oral nimodipine tablets have been used from many years and recommended for vasospasm. But shorter biological half-life (1.7 – 9hrs) (21) makes it difficult in managing blood pressure changes during Triple H or Normotensive therapy for intensive care maintenance of cerebral perfusion blood pressure. Intravenous continuous infusion makes its smoother in controlling the fluctuations of Blood pressure.

The Fischer scale or modified Fischer scale, which is broadly used tool in research studies which also correlated with severity of vasospasm. We concluded from our results that the predictive value of earlier mentioned scale i.e, grade 4 of both Fischer and modified Fischer scale as the worst predictive value. But other studies suggested that grade IV falsely offers the highest predictive value. This might be caused due to variation in population analysed.

By considering modified rankin scale [mRS] as a better tool for predicting outcome in SAH patients, we studied the association of various factors that influence final outcome of the treatment. A score of 5 or above considered as poor outcome and score of less than 5 is considered good outcome. Hypertension and diabetes mellitus have statistically significant and consistent associations with risk of SAH. (Table No 4)

As described management of ruptured intracranial aneurysms, there are two treatment modalities - surgical clipping or endovascular coiling. The International Subarachnoid Aneurysm Trial (ISAT), a multicentre randomized controlled trial, compared endovascular coiling with neurosurgical clipping as treatment for ruptured intracranial aneurysm. [17] Advances in endovascular techniques are making coiling more widely applicable.[18] Majority of our subjects underwent coiling (33 patients;86.54%) and only 5 underwent clipping (13.15%). In the management of acute vasospasm in SAH patient, treatment with oral nimodipine is preferred in many hospital settings. In our hospital, the IV nimodipine in the ICU management and switched over to oral nimodipine after 14 th day of hemorrhage in both microsurgical clipping and endovascular coiling gave promising results which is being depicted in this study. A clinical trial by Erik Kronvall in Lund University Hospital showed that there is no clinically relevant difference in the efficacy between per oral and intravenous administration of nimodipine in preventing delayed ischaemic neurological deficits (DINDs) or cerebral vasospasm following SAH.[19] FDA recommends oral

dosage form and warns against parenteral administration of oral tablets preparations due to serious adverse consequences including cardiac arrest, bradycardia, cardiac collapse, hypertension and death. We used the Intravenous recommended preparation of Nimodipine 0.02% sterile solution in aqueous alcoholic solvent.

Modified rankin scale was used to assess the level of function and we found that the difference in the mRS pre-treatment and follow up scores were significant (0.001). A significant improvement in the mRS score after treatment in majority of patients (only 9 patients poor mRS at the time of follow up of 2 months) were observed.

The assessment of immediate outcome by the Glasgow Coma Score was a useful simple tool in practice. There is no significant difference in the GCS score in the study patient's pre- and post-treatment. The assessment of clinical and neurological improvement after treatment was done by observing improvements in clinical parameters such as blood pressure and heart rate along with neurological deficits. Using paired t test, we found a significant difference in systolic blood pressure (0.001) and no markable difference in heart rate (0.060) between pre- and post-treatment. There was significant neurological improvement in the delayed neurological deficits in patients with vasospasm. For the assessment of radiological improvement, we evaluated CT impressions before and after the treatment. Out of the subjects, 37 patients got resolved by showing resolution of ischemic changes in CT and only one patient did not show any desired improvement from the initial condition. For resolving SAH, the mean duration was obtained as 24.8 days (595.2 hours). Majority of patients had cerebral edema (14 out of 38 patients) followed by infarct (9 patients) and 5 cases of hydrocephalus were reported.

FDA had put forward a Black Box warning regarding the administration of nimodipine intravenously or by any other parenteral routes due to serious life-threatening adverse events including death. In this scenario, we used IV nimodipine recommended preparation with proper monitoring of clinical parameters and dosage; there was no occurrence of serious adverse drug reactions other than correctable hypotension.

Hence, IV nimodipine have better therapeutic effectiveness and showed significant improvement in vasospasm SAH patients. IV Nimodipine exhibited good clinical, Neurological and radiological outcome and would be economically beneficial. The effect of IV nimodipine on improvement of clinical outcome of patients was not studied till date. This study reinforces evidence for the effective use of IV nimodipine over oral nimodipine; that requirement of frequent oral dosage and blood pressure fluctuations between dosages are tide over with intravenous titrated infusions in vasospasm SAH patients. This highlights the importance and advantages of IV nimodipine to treat acute ischaemic vasospasm in SAH patients.

Conclusion

The introduction of IV Nimodipine to the treatment strategy of vasospasm SAH showed significant improvement in the clinical, Neurological and radiological outcomes in the subjects. The Intravenous nimodipine continuous titrated infusions could solve the requirement of frequent oral dosage and blood pressure fluctuations between dosages in the intensive care management of vasospasm in SAH patients.

There was improvement in the quality of life in SAH patients with vasospasm without any life-threatening adverse events other than correctable hypotension in the recommended dose. Intravenous Nimodipine was an effective as an adjuvant in maintenance dosage after endovascular treatment of vasospasm. This is a pilot study evaluation based on the observations but produced good positive outcome and hence we need more randomised control studies for establishing the facts delineated in this study.

Declarations

Ethics approval and consent to participate

The study and Manuscript submission as approved from the Institutional Ethics Committee, Amrita Institute of medical sciences (IEC-AIMS-2018-PHARM-206) and consent forms were obtained from the participants before initiating the study. **All methods** were performed in accordance with the relevant guidelines and regulations

Consent for publication

Approved by the study coordinators as per Institutional guidelines.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Guarantor: Dr. Sreehari N.R.

Competing interests

The authors declare that they have no competing interests.

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Contributions

Sheen Reynold and Aadarsha Sugunan developed the patient data form. Athul Gopan and Athulya Subhash developed the study protocol under the guidance of Dr.Sreehari N R. The sample size and data collection were equally participated by all investigators. The team generated the results and analysed with the help of Dr.Sreehari N R who was the primary treating Physician and concluded the study. Dr. Sajesh K Menon, Head of the Department of Neurosurgery supervised the study throughout. Finally, all the authors have equally contributed to the study. All authors read and approved the final manuscript.

All methods were performed in accordance with the relevant guidelines and regulations approved by the ethics committee.

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Informed consent is been taken from all the study participants. The English format is given below.

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Tables

Table No 1: Mean difference between pre and post clinical parameters.

	Between pre and immediate post treatment	P value
Median SBP ± SD	11.579±14.864	0.000
Median HR ± SD	3.737±11.884	0.060

***Significance at α=0.05**

Table No 2: Mean difference between mRS pre treatment and follow up scores

	Mean difference in mRS ± SD	p value
Between Pre and last follow up phases	1.842± 1.939	0.000

*Significance at α=0.05

Table No 3: Mean difference between pre and post GCS score.

	Mean difference in GCS ± SD	p value
Between Pre and last follow up phases	0.053±0.462	0.487

*Significance at α=0.05

Table No 4: Factors influencing final outcomes.

VARIABLE	NO.OF PATIENTS (%)		OVERALL P VALUE
	GOOD OUTCOME	POOR OUTCOME	
AGE			0.184
<35(2)	2	0	
36-45(6)	5	1	
46-55(10)	10	0	
56-65(12)	9	3	
66-75(5)	3	2	
76-85(3)	3	0	
GENDER			0.357
Male (12)	9	3	
Female(26)	23	3	
HYPERTENSION			0.030
No hypertension (16)	16	0	
Hypertension (22)	16	6	
DIABETES MELLITUS			0.020
No Diabetes mellitus (29)	27	2	
Diabetes mellitus (9)	5	4	
WFNS			
Grade IV	2	1	
Grade V	0	0	
modified Fischer scale			0.127
0/I (6)	5	1	
II (4)	4	0	
III (16)	15	1	
IV (10)	6	4	
Fischer scale			0.178
I/II	5	0	
III	3	0	

IV	10	1