Importance of the Return of Nimodipine to Brazil: pharmacological options for cerebral vasospasm after subarachnoid hemorrhage. Literature review

ABSTRACT

Introduction: Cerebral vasospasm refers to the narrowing or reduction in diameter of cerebral arteries occurring after management of aneurysmal subarachnoid hemorrhage. As a consequence of this vasospasm, there is delayed cerebral ischemia, which generates neurological impairment. The use of Nimodipine is the main indication with level of evidence A and class of recommendation 1, presenting benefits in prevention and improving functional results. Furthermore, Brazil does not import or manufacture nimodipine itself. Objective: To review the literature on all oral and intravenous medications for preventing cerebral vasospasm after subarachnoid hemorrhage and present the lack of this medication in Brazil. Results: Nimodipine demonstrated efficacy in reducing cerebral vasospasm after aneurysmal subarachnoid hemorrhage, although it did not demonstrate a significant reduction in mortality. Other medications, such as Milrinone, Clazosentan, Cilostazol, and Statins have also shown benefits, but their effectiveness and safety may vary depending on the patient’s individual circumstances. Conclusion: Nimodipine is the best proven medication and is not present in Brazil in any form of administration and, therefore, appropriate measures must be taken.

Keywords: Intracranial vasospasm; Aneurysmal subarachnoid hemorrhage; Nimodipine; Brain ischemia

RESUMO

Introdução: Vasoespasmo cerebral refere-se ao estreitamento ou redução do diâmetro das artérias cerebrais ocorrendo pós manejo de hemorragia subaracnoidea aneurismática. Como consequência desse vasoespasmo, há isquemia cerebral tardia, que gera comprometimento neurológico. O uso de Nimodipino é o principal indicado com nível de evidência A e classe de recomendação 1, apresentando benefícios na prevenção e melhorando os resultados funcionais. Ademais, o Brasil não possui importação nem fabricação própria do nimodipino. Objetivo: Revisar a literatura de todos os medicamentos orais e endovenosos para prevenção de vasoespasmo cerebral pós-hemorragia subaracnoide e apresentar a falta desse medicamento no Brasil. Resultados: O nimodipino demonstrou eficácia na redução do vasoespasmo cerebral pós-hemorragia subaracnoide aneurismática, embora não tenha demonstrado redução significativa na mortalidade. Outros medicamentos, como milrinone, clazosentan, cilostazol e estatinas também apresentaram benefícios, mas sua eficácia e segurança podem variar dependendo das circunstâncias individuais do paciente. Conclusão: O nimodipino é o medicamento com melhor comprovação e não está presente no Brasil em nenhuma forma de administração e, portanto, medidas cabíveis devem ser tomadas.

Palavras-chave: Vasoespasmo intracraniano; Hemorragia subaracnoidea aneurismática; Nimodipino; Isquemia encefálica

Received Oct 30, 2023
Corrected Jan 5, 2024
Accepted Jan 5, 2024

Chaves SCS, Vitalino DPS, Silva Junior LF, Santos AM, Silva PLM, Brandão HS, Safatle RL - Importance of the Return of Nimodipine to Brazil: pharmacological options for cerebral vasospasm after subarachnoid hemorrhage. Literature review

https://doi.org/10.22290/jbnc.2024.350110
INTRODUCTION

Cerebral vasospasm refers to the narrowing or reduction in the diameter of the cerebral arteries occurring after management of aneurysmal subarachnoid hemorrhage (aSAH), constituting one of the biggest management challenges and being the biggest contributor to morbidity and mortality. It occurs in about 30% of patients, between the fourth and fourteenth day after SAH, so that several mechanisms have been implicated for the progression of vasospasm, such as decreased production of nitric oxide (NO) in the endothelium and degradation of hemoglobin (Hb) which leads to an increase in endothelin-12.

As a consequence of this vasospasm, there is delayed cerebral ischemia (TI) that generates focal neurological impairment or a drop of at least 2 points on the Glasgow Coma Scale (ECG), which must last at least one hour. Because of this, effective treatment is necessary as a mean of preventing STI.

In this case, the use of Nimodipine is the main indication with level of evidence A and class of recommendation 1, presenting benefits in the prevention of STI and improving functional results. Nimodipine is an antagonist of slow calcium channels of the dihydropyridine class, of the calcium channel blocker class, consequently relaxing the cerebral vasculature.

This article is unprecedented, as no Brazilian review has a comprehensive discussion of all available medications for vasospasm after subarachnoid hemorrhage, nor does it discuss the lack of this medication in our country.

MATERIAL AND METHODS

The search was carried out in the Virtual Health Library (VHL), Latin American and Caribbean Literature in Health Sciences (LiLACS), PubMed and Scopus databases, and was limited to articles between the period 2018 to 2023 that met the criteria of being literature reviews, systematic reviews with or without meta-analysis, randomized clinical trials or not, or case reports or series.

The search strategy used was: “pharmacological treatment” AND “cerebral vasospasm” AND “subarachnoid hemorrhage”; identical in all database searches.

Then, duplicated articles and those that did not have the full text free and available for reading were excluded. Thus, the titles and summaries of the articles were analyzed independently by each of the authors, with those whose themes fit this research being selected, with two authors who analyzed the same database. Then, if there were doubts about whether it would fit into this research, the article was decided by a third author independently.

In the end, 27 articles were selected for complete reading and composition of this literature review, in addition to 3 reference articles from the current guideline on the subject, which was also included manually, totaling 31 scientific works (Figure 1).

RESULTS

The effectiveness of nimodipine in the treatment of cerebral vasospasm has been extensively studied and compared with other medications in several clinical studies. In this context, we will discuss the results of these studies and compare nimodipine with other relevant medications.

Effectiveness of nimodipine

Initially, it is noteworthy that nimodipine, according to a literature review conducted by Chugh and Agarwal, although it is a calcium channel blocker, acts through several other mechanisms that help reduce the incidence of cerebral vasospasm and delayed cerebral ischemia, namely an effect neuroprotective, reducing the death of neuronal cells, the intracellular influx of calcium and improving blood viscosity. Some studies have also demonstrated an antiplatelet effect and dilation of the collateral circulation of the leptomeninges, which also contribute to this neuroprotective effect.
Several studies have highlighted the efficacy of nimodipine in the prophylactic treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. In a controlled study by Lee et al.\(^1\), which involved 554 patients, nimodipine demonstrated a significant reduction in the incidence of cerebral arterial spasm compared to the control group (21% vs. 42%, respectively). Furthermore, nimodipine treatment improved neurological outcomes within 3 months after subarachnoid hemorrhage. However, there was no specific information about morbidity or mortality associated with the use of nimodipine in this study.

According to a review by Dayyani et al.\(^5\), nimodipine is effective in reducing cerebral vasospasm (OR, 0.59 [95% CI, 0.36–0.97]; Absolute Risk Reduction (ARR), −13.10% [95% CI, −0.74 to −24.81]), is likely to reduce mortality when compared to placebo (OR, 0.73 [95% CI, 0.53–1.00]; moderate certainty; ARR, −3.35% [95% CI, −6.00 to −0.00]) and was effective (OR, 1.46 [95% CI, 1.07–1.99]; high certainty; absolute risk increase, 8.25% [95% CI, 1.55–14.09]) in improving the level of disability at follow-up.

Furthermore, a systematic review and meta-analysis conducted by Lukito et al.\(^6\), concluded that nimodipine significantly reduced the incidence of symptomatic vasospasm and improved clinical outcomes in patients with aneurysmal subarachnoid hemorrhage. However, nimodipine did not significantly reduce mortality in patients with aSAH. Importantly, the use of nimodipine was associated with an increased incidence of hypotension compared to the control group.

Regarding the duration of treatment, in the study by Sokolowski et al.\(^7\), in which 60mg of oral nimodipine was administered 4 times a day, the duration of less than 14 days or between 15 and 20 days was not inferior when compared to the 21-day treatment, in terms of reducing vasospasm, good functional score and readmission due to stroke.

According to the study Carlson et al.\(^3\), in relation to the routes of administration, comparing oral nimodipine with intraventricular nimodipine EG-1962, there was no increase in favorable prognoses with 600mg intraventricular nimodipine. Individuals with grade 2
on the World Federation of Neurological Surgeons scale had more favorable results using oral nimodipine, while individuals with grades 3-4 had better results with EG-1962. Regarding adverse effects, hypotension was less common and hydrocephalus was more common in the intraventricular nimodipine group.

Comparison with other medicines

Milrinone

Studies by Abulhasan et al.8 and Castle-Kirschbaum et al.9 demonstrated the use of milrinone in the treatment of refractory cerebral vasospasm. The results suggested a significant reduction in morbidity and mortality in patients treated with milrinone. Furthermore, according to Crespy et al.10, milrinone, which is an inhibitor of phosphodiesterase (PDE) III2, is effective in reversing vasospasm segments and, regardless of the protocol (intravenous administration or intra-arterial/intravenous administration), generates good prognoses regarding neurological deficits. The need for rescue procedures (nimodipine administration, additional milrinone infusion or mechanical angioplasty) for persistence or recurrence of vasospasm was similar in both protocols.

Clazosentan

The study by Cho et al.11, from 2019, evaluated that clazosentan demonstrated to be effective in reducing Late Ischemic Neurological Deficit. Regarding mortality and morbidity at 6 months related to vasospasm in patients after SAH, there was a lower occurrence of events with the use of clazosentan, compared to placebo, but without statistical significance (adjusted RR, 0.81; 95% CI, 0.70 - 0.94; diversity D2 = 74%). Clazosentan administration also reduced angiographic vasospasm. Bruder et al.12 and Endo et al.13, in 2022, highlighted clazosentan as a medication that reduces the incidence and severity of cerebral vasospasm. CONSCIOUS-1 and CONSCIOUS-2 showed benefits regarding the incidence of cerebral infarction and vasospasm-related morbidity in patients with aneurysmal subarachnoid hemorrhage. However, results varied depending on factors such as the severity of the hemorrhage and the presence of comorbidities. The efficacy of clazosentan was directly compared with nimodipine in a large randomized study by Endo et al.13, and showed no significant benefit in mortality or morbidity. The study by Maruhashi et al.14, also suggests an increase in adverse effects with the use of clazosentan.

Cilostazol

Study by Liu et al.15, investigated cilostazol in the treatment of aneurysmal subarachnoid hemorrhage and reported that the medication can reduce cerebral vasospasm. In review by Dayyani et al.16, cilostazol showed low certainty regarding the reduction of cerebral vasospasm (OR, 0.39 [95% CI, 0.19–0.79]; ARR, –23.01% [95% CI, –5.82 to –37.26]). Furthermore, a meta-analysis showed that treatment with antiplatelet agents, including cilostazol, reduced the occurrence of delayed cerebral ischemia and symptomatic vasospasm. However, it is important to note that more studies are needed to confirm the effectiveness of cilostazol.

Ozagrel

The study by Bhat et al.17, highlighted, in a retrospective analysis of patient outcomes that there were more patients with preoperative vasospasm in the group that used ozagrel at a dose of 80mg/day, intravenously, than in the placebo group. However, considering the subgroup with preoperative vasospasm, the positive outcome was greater in the ozagrel group.

Statins

The 2021 study by Maruhashi et al.14, in its review, highlighted that the use of statins does not influence the clinical outcome, but can reduce vasospasm. In the study by Chen et al.18, the use of 20mg/day of atorvastatin associated with Nimodipine in elderly patients, reduced the occurrence of postoperative cerebral vasospasm (RR 1.397, 95% CI 1.11 - 1.76). Furthermore, in 2023, they reported that statins significantly reduced the incidence of ischemic cerebrovascular events in patients with aneurysmal subarachnoid hemorrhage. Pravastatin was identified as the most effective. In a controlled study by Maruhashi et al.14, a lower incidence of severe cerebral vasospasm occurred in the group that used pitavastatin than in the group that used placebo. However, there was no specific information on the morbidity and mortality associated with the use of statins in patients with aneurysmal subarachnoid hemorrhage. Regarding statins, there may be beneficial effects in the treatment of cerebral vasospasm, but without benefit in the long-term outcome.

Magnesium sulfate

According to Soliman et al.19, magnesium sulfate is effective in reducing cerebral vasospasm (OR, 0.61 [95% CI, 0.41–0.92]; ARR – 12.27% [95% CI, –2.04 to –21.86]). The review by Maruhashi et al.14 highlighted that the combination of intracisternal magnesium sulfate with intravenous hydrogen infusion also reduced vasospasm. Furthermore, in a randomized clinical trial with 90 patients18, they compared the prophylactic effect of magnesium sulfate and intravenous milrinone on the incidence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage.
(aSAH), in which one group received magnesium sulfate in infusion of 500 mg for 24 hours (daily), without a loading dose after the diagnosis of aSAH for 21 days and another received milrinone in an infusion of 0.5 g/kg/1 min (for 24 hours daily), without dose of attack for 21 days. The authors found that the group that received magnesium had a lower incidence of cerebral vasospasm after aSAH, as well as hypotension and the need for postoperative mechanical ventilation, in addition to significantly improving the Glasgow Coma Scale. Neurological outcome (GCS) was better in the magnesium group than in the milrinone group. The study showed that intravenous milrinone has no effect on the incidence of cerebral vasospasms and that it was associated with significant hypotension, requiring the administration of norepinephrine and dopamine.

Nicardipine

Dayani et al.5, mentioned that nicardipine can reduce cerebral vasospasm (OR, 0.37 [95% CI 0.17–0.79]; low certainty; ARR, −24.20% [95% CI, −5.82 to −39.05]. In the review by Maruhashi et al.14, nicardipine, through prolonged-release implants, which are restricted to patients who had surgical clipping of the aneurysm, reduced angiographic vasospasm and improved neurological outcomes and mortality.

Fasudil

Maruhashi et al.14 showed that the incidence of symptomatic and angiographic vasospasms was lower with the use of fasudil, when compared to those who did not receive the treatment, in addition to that there was a reduction in low-density regions related to vasospasm on CT.

Non-steroidal anti-inflammatory drugs

Solar et al.19 highlighted selective COX-2 inhibitors, such as celecoxib and meloxicam, which can potentially serve as agents for the prevention of cerebral vasospasms after SAH. The use of 7.5 mg of meloxicam twice a day for seven days resulted in a lower incidence of vasospasm and mortality, shorter hospital stay and improved GOS, but without statistical significance when compared to placebo.

Heparin

In 2022, Marazzi et al.20, the usage of low-dose intravenous heparin infusion (8 U/kg/hour progressing after 36 hours to 10 U/kg/hour) in patients with aneurysmal subarachnoid hemorrhage as a treatment for vasospasm and prevention of late cerebral ischemia, in a retrospectively controlled study with 39 patients led to a reduction in the occurrence of vasospasm and late cerebral ischemia in the intervention group without any intensification of bleeding. In this sense, these results indicate the participation of microthrombotic mechanisms in the cerebral vasculature in the pathophysiology of delayed cerebral ischemia and cerebral vasospasm. Furthermore, in the review by Maruhashi et al.14, enoxaparin significantly reduced the risk of cerebral vasospasm.

Nitroglycerin

According to a case series and literature review by Gatto et al.21, nitroglycerin reduces cerebral blood flow, reduces mean arterial pressure, dilates spastic arteries and reduces the clinical occurrence of late ischemic neurological deficits. However, usual clinical doses can lead to the “theft phenomenon”, that is, leading to the dilation of intact arteries. At a low dose, it significantly improved vasospasm without significant changes in systemic circulation. Systemic administration may induce the development of tolerance, as well as the phenomenon of rebound hypertension after drug discontinuation. The main disadvantages of intrathecal use: its time of action (residual effect up to 5 days), which, if used in higher doses, breaks the blood-brain barrier causing toxicity and cerebral infarction.

Nitric oxide analogues

According to Chugh and Agarwal4, nitric oxide (NO) is a potent vasodilator and its role in cerebral vasospasm has been extensively studied. Blood degradation products decrease endothelial NO production and impair its effects on the vascular endothelium, leading to vasoconstriction. Therefore, theoretically, NO analogues should help with vasodilation, increasing NO production. NO donors, such as sodium nitrite (NaNO₂), have been studied in animals and demonstrated a promising effect on vasodilation. The role of adinopectin in subarachnoid hemorrhage has been reported by some studies. It has been postulated that adinopectin causes activation of AMP-activated protein kinase α and the endothelial NO synthase signaling pathway. L-citrulline has been found to be safe and effective in some experimental studies. It has been shown to increase e-NOS expression and therefore NO availability. However, the use of NO analogues for the treatment of cerebral vasospasm resulting from aneurysmal subarachnoid hemorrhage is still in the experimental phase 2.

Thus, nimodipine demonstrated efficacy in reducing cerebral vasospasm after aneurysmal subarachnoid hemorrhage, although it did not demonstrate a significant reduction in mortality. Other medications, such as milrinone, clazosentan, cilostazol, and
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In addition to no longer having national production of this medicine, imports are at the mercy of large, financially favored centers and production is also manipulated in these centers for use in their patients. On the other hand, throughout the rest of Brazil it is lacking.

The lack of this medication can compromise the quality of life, as delayed cerebral ischemia, resulting from the vasospasm process, is highly capable of causing dysfunctionality to the individual and, therefore, is a public health issue that we must fight for, in order to bring this medicine back to our country.

DISCUSSION

Enteral nimodipine is present in the 2023 American Heart Association/American Stroke Association guideline as the highest level of evidence (1A) for the prevention of cerebral vasospasm after aneurysmal subarachnoid hemorrhage.

Also according to the 2023 guideline, although studies of intravenous and intra-arterial nimodipine have been reported, there are limited data to make any recommendations for these routes of administration of nimodipine.

Furthermore, there are also primary studies on the use of topical nimodipine, directly on the affected vessel, to prevent vasospasm. However, the low evidence only reinforces that oral nimodipine is greatly missed in our country.

The pharmaceutical industry in Goiás VITAMEDIC, one of those responsible for a large percentage of nimodipine production in Brazil, on 08/30/2022, discontinued its production for reasons of 'manufacturing process', according to the Medicines Discontinuation Panel, present on the website of ANVISA.

Having explained the entire situation, Brazil is currently using second- or third-line proven medications for the prevention or treatment of cerebral vasospasm, such as labetalol, nicardipine, esmolol, hydralazine, enalapril and nitroprusside. In this sense, they emphasize that the most used drug and with the best scientific evidence to perform percutaneous transluminal chemical angioplasty for the treatment of cerebral vasospasm is nimodipine, however its injectable formulation is not approved by the National Health Surveillance Agency (Anvisa) in Brazil. Alternative options, which include milrinone, verapamil, nicardipine, among others, are not available in the Unified Health System (SUS), being reserved only for patients seeking treatment in the private sector. Furthermore, the use of papaverine is currently discouraged due to possible neurotoxicity and risk of intracranial hypertension. Therefore, only nitroglycerin, although not the best choice for treating cerebral vasospasm, is the only one available in the country in many locations.

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The lack of this medication can compromise the quality of life, as delayed cerebral ischemia, resulting from the vasospasm process, is highly capable of causing dysfunctionality to the individual and, therefore, is a public health issue that we must fight for, in order to bring this medicine back to our country.

CONCLUSION

Nimodipine is the medication with the best evidence for improving the occurrence of cerebral vasospasm after subarachnoid hemorrhage and, consequently, preventing delayed cerebral ischemia and transient or permanent sequelae. This medicine is not present in Brazil in any form of administration and, therefore, appropriate measures must be taken.

REFERENCES


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Funding: Conflicts of interest.
Conflicts of interest: nothing to disclose.
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