THE IMPACT OF REVASCULARIZATION SURGERY ON HEADACHE IN PATIENTS WITH MOYAMOYA

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Abbreviations

MMV= moyamoya vasculopathy
EC-IC= extracranial-intracranial
CVR= cerebrovascular reactivity
MRI= magnetic resonance imaging
UHN= University Health Network

Abstract

Background and Aims: Significant headache in moyamoya vasculopathy is not uncommon but the pathophysiology is poorly understood. We aimed to investigate if headache in moyamoya patients improves after revascularization surgery and whether this is associated with improvement in cerebrovascular reactivity.

Methods: For this single-center retrospective study, adult patients with moyamoya vasculopathy who underwent extracranial-intracranial bypass surgery between January-2010 and September-2022 were selected from a database with consecutive patients who had MRI with cerebrovascular reactivity studies. Clinical data including a headache history and imaging data were collected through systematic chart review. We assessed the association between headache and cerebrovascular reactivity before and after uni- or bilateral revascularization surgery.

Results: Fifty-one patients were included (mean age 42±13 years, 37 women (73%)). Thirty-three patients (65%) had bilateral moyamoya vasculopathy and 14 (27.5%) underwent bilateral extracranial-intracranial bypass surgery. Thirty-five patients (69%) reported headache pre-surgery. Features included: episodic headache (96%), preceding aura (12%),

predominantly throbbing headache (47%) with nausea/vomiting (39%), and/or photo/phonophobia (11%); 62% of patients lost workdays because of headache. Headache improved in 24/35 (69%) patients after surgery with reduction in pain severity (median VAS from 7 to 3; p <0.01) and sick leave (62% to 19%; p=0.0024). CVR improved in 25/38 (66%) patients who had pre- and post-surgery CVR-MRI, which was associated with headache improvement (OR:13; 95%CI: 1.3-124). Younger age was also associated with headache improvement post-surgery (OR:0.88; 95%CI: 0.81-0.96).
Conclusions: Headache in moyamoya vasculopathy improved in most patients after revascularization surgery and was associated with improvement in cerebrovascular reactivity, supporting the hypothesis of a vascular origin of the headache.

1. Introduction

Moyamoya vasculopathy (MMV) is a chronic cerebrovascular disease, characterised by progressive stenosis of the terminal portion of the internal carotid artery and the main branches with compensatory collateral vessels, so-called ‘moyamoya’ vessels.[1-3] MMV includes both moyamoya disease and moyamoya syndrome. The latter differs from moyamoya disease by having an associated medical condition whereas moyamoya disease is idiopathic.[2] Moyamoya vasculopathy can cause ischemic stroke and intracranial hemorrhage with a high rate of disability and even death.[2][4-8] Treatment consists of medical management and in select cases brain surgery, most commonly extracranial-intracranial arterial bypass surgery (EC-IC bypass surgery), to help prevent ischaemic or hemorrhagic stroke.[2][4][5][7]

MMV can cause hypoperfusion in affected parts of the brain, which increases the risk of stroke. The severity of hypoperfusion and the availability of vascular reserve to compensate for it, can be measured with magnetic resonance imaging (MRI) with cerebrovascular reactivity study (CVR).[9-12] This imaging study is standard of care in patients with moyamoya vasculopathy at University Health Network (UHN).

In clinical practice, physicians focus on stroke-like symptoms in patients with moyamoya vasculopathy to decide on the indication for revascularization therapy, i.e. brain surgery.[4][13-18] In the revascularization clinic at UHN, we noted that a significant number of patients with moyamoya vasculopathy report disabling headaches. The mechanism of the headache is not well understood but may be related to hypoperfusion and impaired cerebrovascular reactivity, since we may see an improvement of the headache after revascularization therapy.

There is limited data available on a potential association between brain perfusion status and headaches in patients with moyamoya vasculopathy whereas chronic headaches have a significant impact on quality of life and carry a high financial burden.[19-25]

Therefore, the aim of this study is to investigate if headache in moyamoya patients improves after revascularization surgery and whether this is associated with improvement in cerebrovascular reactivity.

2. Methods

2.1 Participants

This retrospective study includes MMV patients who underwent EC-IC bypass surgery. They were selected from a database of consecutive patients who had MRI with CVR studies at the University Health Network *(Fig. 1)*.

Inclusion criteria: Adults (≥ 18 years) with unilateral or bilateral MMV with at least one MRI with CVR study obtained between 2010 and 2022 and who had EC-IC bypass surgery between January 2010 to September 2022.

Exclusion criteria: Patients with a lack of headache data in medical records and survey research.

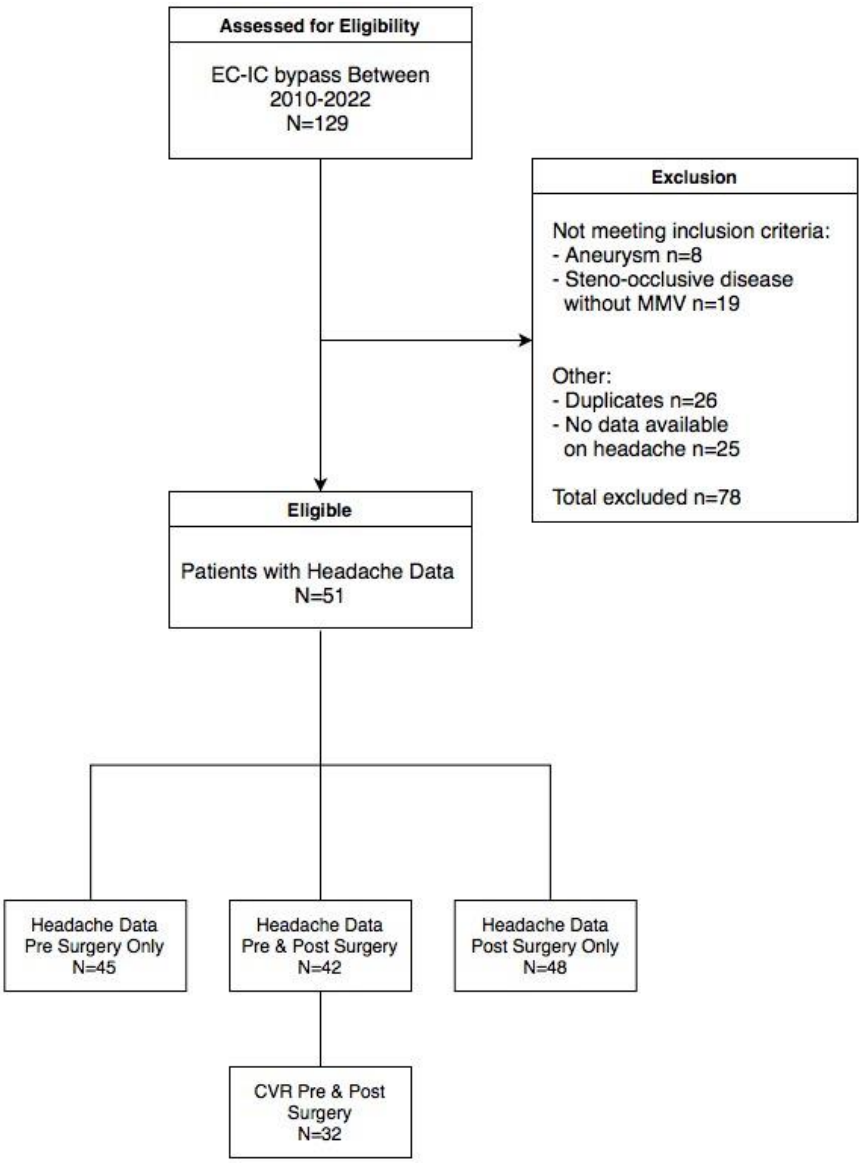


Figure 1 Flowchart of the patients included in the study
EC-IC= extracranial-intracranial, MMV=moyamoya vasculopathy

2.2 Study design

This retrospective single-centre study was conducted at UHN. The data were collected retrospectively through chart review and included gender, age, diagnosis, blood-pressure values, comorbidities, presence of headache, headache severity, headache localization, side of EC-IC bypass surgery, date of last EC-IC bypass surgery, peri-operative complications, MRI-CVR-dates, the affected artery or arteries and MRI-CVR study reports before and/or after EC-IC bypass surgery.

Additional headache data was collected pre- and post-surgery through a standard of care cross-sectional structured survey. This included, presence of headache, headache severity, headache

localization, type of headache, triggering factors, warning signs, accompanying symptoms, depression, use of painkillers and the impact on work.
The Research Ethics Board of our centre approved the study and provided permission to review patients' medical records and to use the corresponding data. The need for informed consent was waived due to the retrospective nature of the study.

2.3 Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables and as numbers and percentage for categorical variables. We used the McNemar-Bower test to compare proportions and the Wilcoxon signed rank test to compare pain scores (VAS) pre- and post-surgery. This was followed by the calculation of odds ratios with corresponding 95% confidence intervals (95%CI) to explore the association between improvement of headache and improvement of cerebrovascular reactivity after surgery. We used exploratory logistic regression analysis to determine potential predictors for improvement of headache after surgery. A p value <0.05 was considered statistically significant. The data were statistically analysed using SPSS version 28 software.

3. Results

3.1 Participants' Characteristics

Patient baseline demographic and clinical characteristics are shown in *table 1.*

Table 1. Baseline Characteristics of the Patients

ICA= internal carotid artery, MCA= middle cerebral artery, PC= posterior circulation, ACA= anterior cerebral artery, TIA=transient ischemic attack.
Types of bypass surgery:
EC-IC bypass = extracranial-intracranial bypass
EDAS= encephaloduroarteriosynangiosis

Characteristics	**Patients with headache data N= 51**
Age (yr)	42 ± 13
Female sex n (%)	37 (73%)
Diagnosis n (%)	
Moyamoya disease	34 (67%)
Moyamoya syndrome	17 (33%)
History of stroke n (%)	

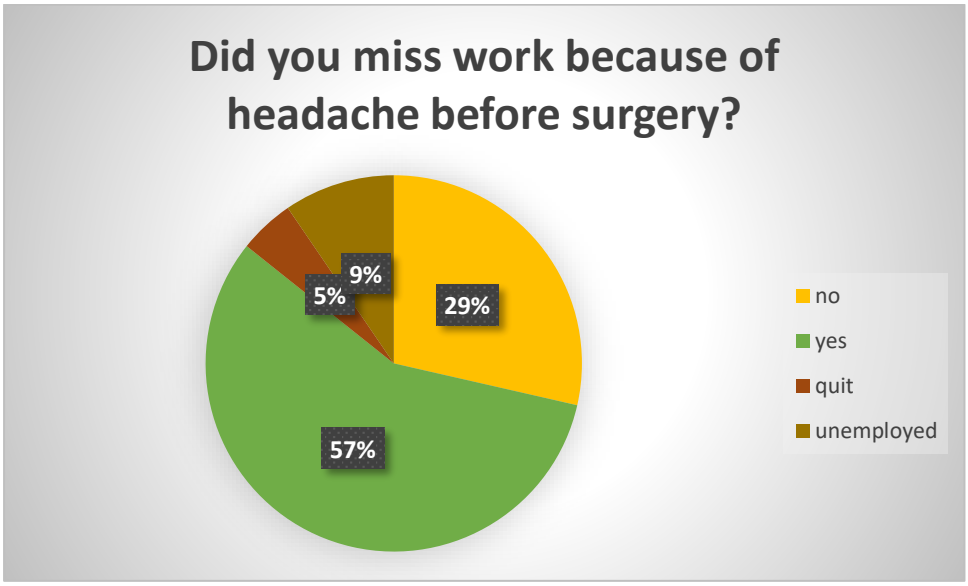
Only ischemic	30 (60%)
Only hemorrhagic	4 (8%)
Ischemic and hemorrhagic	9 (18%)
No history of stroke	7 (14%)
Affected artery n (%)	
ICA	**42 (82,3%)**
Left	7 (13.7%)
Right	9 (17.6%)
Bilateral	26 (51.0%)
MCA	**21 (41,1%)**
Left	7(13.7%)
Right	4(7.8%)
Bilateral	10(19.6%)
PC	**3 (5.9%)**
Left	1 (2.0%)
Right	0 (0.0%)
Bilateral	2 (3.9%)
ACA	**12 (23,5%)**
Left	5 (9.8%)
Right	2 (3.9%)
Bilateral	5 (9.8%)
Bypass surgery n (%)	
EC-IC bypass left	17 (33.3%)
EC-IC bypass right	17 (33.3%)
EC-IC bypass bilateral	14 (27.5%)
EDAS	3 (5.9%)
Complications of surgery n (%)	**13 (25,4%)**
Post operation infection	2 (3.9%)
Hemorrhage	3 (5.9%)
Intra/post operation seizures	2 (3.9%)
Post operation TIA's	2 (3.9%)
Post operation ischemic stroke	4 (7.8%)

In this study 129 patients were assessed for eligibility, hereof 51 met the inclusion criteria and were included in the final analysis (Fig. 1). The patients' mean age was 42 ± 13 years and the majority of the patients were females (73%). Sixty-seven percent of the patients were diagnosed with moyamoya disease and 33% with moyamoya syndrome. In regard to their stroke history

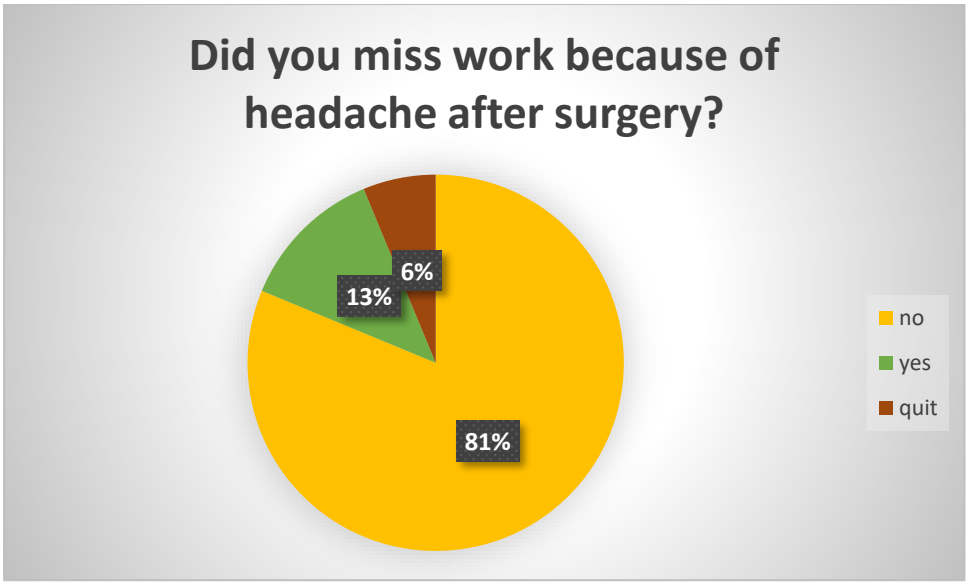
60% of the patients had mainly suffered an ischemic stroke only, 8% a hemorrhagic stroke only, 18% had both ischemic and hemorrhagic stroke and 14% patients had no history of stroke. Predominantly the internal carotid artery (n=42, 82%) and the middle carotid artery (n=21, 41.1%) were affected. Thirty-three patients (65%) were diagnosed with bilateral moyamoya arteriopathy and 14 (27.5%) underwent bilateral EC-IC bypass surgery. Twenty-five percent of the patients had a surgical complication (Table 1).

3.2 Headache characteristics and changes post-surgery

Thirty-five patients (69%) reported headaches pre-surgery. Headache characteristics were mainly reported to be throbbing in forty-seven percent (Fig. 2) and episodic in 96%. Twelve percent of the patients had preceding aura and in 39% the headache was accompanied by nausea/vomiting and/or in 11% of the patients by photo/phonophobia. In 69% (n=24) of the patients there was an improvement of the headache after surgery with a decrease in pain severity from a median visual analogue scale of 7 to 3 ($p<0.01$). Furthermore, the CVR-MRI improved post-surgery in 66% (25 of 38 patients) of the patients which was associated with a statistically significant headache improvement (OR 13; 95%CI: 1.3-124). Additionally, younger age was independently associated with headache improvement post-surgery (OR:0.88; 95%CI: 0.81-0.96). Moreover, there was a reduction of 62% to 19% (p=0.0024) in sick leave (Fig. 2) and of pain medication use from 81% to 45% post-surgery.



2.A



2.B

Figure 2. A Sick leave pre-surgery, B Sick leave post-surgery

4. Discussion

In this study we found an improvement of headache after revascularization surgery with a significant reduction in pain severity. Furthermore, we found a significant decrease in sick leave and reduced painkiller use after surgery. In addition, we saw that CVR improved after surgery which was associated with significant headache improvement. Younger age was also associated with headache improvement post-surgery. Another finding of this study is that the clinical features of headache were predominantly migraine-like.

To our knowledge there are scarce studies researching the effect of revascularization therapy on headache in adult MMV patients. However, significant headache is common in these patients and has a serious impact on quality of life.[26-27]

The pathophysiology of headache in MMV patients is not well understood. There is different hypothesis on this matter.[28][29] MMV leads to progressive stenosis and occlusion in the terminal portion of the internal carotid artery and its main branches. This results in cerebral hypoperfusion leading to hypoxia and microvascular ischemia, resulting in impaired cerebral hemodynamics which could be a possible cause of headache in MMV patients. In addition, microvascular ischemia could generate cortical spreading depression which could lead to migraine with aura. [27][28][30]

Our study supports this hypothesis by showing that an improvement of CVR after revascularization surgery was associated with a statistically significant improvement of headache. The hypothesis of a vascular origin causing headache in MMV patients is also

supported by several case studies showing an amelioration of headache after improving cerebral perfusion with revascularization therapy.[27][28][31] This finding is also in line with the study of Kawabori et al. which reported that an impaired CVR was a significant predictor for headache in pediatric patients with MMV (p=0.028).[26]

A Chinese observational study (Gao et al.) showed no differences in long term outcomes of headache between MMV patients who underwent revascularization therapy and those who had conservative treatment.[32] EC-IC bypass is only done in cases where the disease is more advanced to help prevent ischaemic or hemorrhagic stroke.[4][13-18] Patients who underwent conservative treatment probably had a less progressed MMV and therefore better cerebrovascular hemodynamics. The short-outcome results in this study did prove a significant headache improvement after revascularization therapy. The difference between the short- and long-term outcomes could possibly also be explained by progression of MMV disease. In our study a younger age was associated with significant headache improvement post-surgery, whereas older patients had significantly more headache, which could be related to having a more advanced stage of MMV, supporting previous theory. Kawabori et al. showed that the Suzuki angiographic stage in the hemispheres with headache was significantly more advanced than in those without (p=0.029), indicating that progression of the disease is associated with headache.[26] Future studies could explore at which Suzuki staging the patient will benefit the most from revascularization surgery in regard to their headaches.

Furthermore, our study showed that 69% of patients with MMV reported headaches before revascularization surgery. Clinical features of headache were episodic (96%), throbbing (47%) and were accompanied by nausea/vomiting (39)% and preceding aura (12%), which is similar to migraine-like features. These findings of MMV patients with predominantly migraine-like phenotype headaches are supported by the study of Gao et al. and Kreamer et al., were migraine-like headaches were reported in respectively 75.5% and 72.9% of the MMV patients.[27][32] Therefore, in patients with migraine that is therapy resistant or has atypical features such as a higher age of onset, an underlying cause as MMV could be considered and explored with a noninvasive angiogram.

Moreover, our study showed how incapacitating headache in MMV patients is, resulting in a median VAS of 7 and a sick leave of 62% before surgery. The study of Kawabori et al. reported a decrease in school attendance under all pediatric patients who had headaches before revascularization surgery.[26] Emphasizing how negatively this serious symptom of MMV interferes with essential daily activities of MMV patients.

In this study, the effect of revascularization therapy on headache change in MMV patients was analysed. We saw a successful decrease of sick leave and headache severity, denoting the improvement of quality of life in these patients. Improvement of headache after revascularization surgery is an added benefit that should not be underestimated.

The strengths of this study are the size of patients we were able to include despite the rarity of MMV and our database and structured questionnaires from which we were able to subtract sufficient clinical characteristics. In terms of limitations in our study we must address the recall bias due to the retrospective nature of the study.
These study results are hypothesis generating and will need to be reproduced in a larger cohort of patients with MMV in a prospective manner to mitigate recall bias. Once the pathophysiology of this disabling headache is better understood, treatment targets may be identified to tailor headache management in this patient population.

5. Conclusion

Headache in moyamoya vasculopathy improved in most patients after revascularization surgery and was associated with improvement in cerebrovascular reactivity. This supports the postulation that headache in patients with moyamoya vasculopathy has a vascular origin.

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