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Surgical timing and long-term outcomes in patients with severe haemorrhagic spinal cord cavernous malformations

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ABSTRACT

Background Surgical resection of the lesions remains the main treatment method for most symptomatic spinal cord cavernous malformations (SCCMs) to eliminate the occupation and associated subsequent lifelong haemorrhagic risk. However, the timing of surgical intervention remains controversial, especially for patients in the acute stage after severe haemorrhage.

Methods Patients diagnosed with SCCMs who were surgically treated between January 2002 and December 2021 were selected and retrospectively reviewed. The Modified McCormick Scale (MMS) was used to evaluate neurological and disability status. All medical information was reviewed, and all patients were followed up for at least 6 months.

Results A total of 279 patients were ultimately included. With regard to long-term outcomes, 110 (39.4%) patients improved, 159 (57.0%) remained unchanged and 10 (3.6%) worsened. For patients with an MMS score of 2–5 on admission, in univariate and multivariate analyses, a ≤6 weeks period between onset and surgery (adjusted OR 3.211, 95% CI 1.504 to 6.856, p=0.003) was a significant predictor of improved MMS. Among 69 patients who first presented with severe haemorrhage, undergoing surgery within 6 weeks of the onset of severe haemorrhage (adjusted OR 4.901, 95% CI 1.126 to 21.325, p=0.034) was significantly associated with improvement of MMS score.

Conclusion Surgical timing can influence the long-term outcome of SCCMs. For patients with symptomatic SCCMs, especially those with severe haemorrhage, early surgical intervention within 6 weeks can provide more benefit.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Spinal cord cavernous malformations (SCCMs) are rare low-flow vascular malformations which are mainly treated by surgical resection. Several large series have discussed the natural history and long-term outcomes of SCCMs. However, the optimal timing for surgical intervention, particularly for patients experiencing severe haemorrhage in the acute stage, remains controversial.

WHAT THIS STUDY ADDS

⇒ Our study revealed that early surgical intervention, within 6 weeks, for symptomatic SCCMs, particularly in patients with severe haemorrhage, resulted in improved long-term outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ For patients with symptomatic SCCMs, early diagnosis and surgery or referral should be considered, as it could result in better long-term outcomes.

INTRODUCTION

Spinal cord cavernous malformations (SCCMs) are rare low-flow vascular malformations, accounting for 5%–12% of all spinal vascular diseases.[1–3] Compared with their intracranial counterparts, SCCMs are more aggressive because the narrow spinal cavity contributes to a low tolerance for space-occupying lesions.[4–6] Resection of the lesions remains the main treatment method for most symptomatic SCCMs to eliminate the lesion and associated subsequent lifelong haemorrhagic risk.[7 8] The natural history and long-term outcomes of SCCMs have been discussed, especially in several large series.[4 9] However, the timing of surgical intervention remains controversial, especially for patients in the acute stage after severe haemorrhage. In this study, we reviewed 279 surgically treated symptomatic SCCMs with long-term follow-up, which included 69 patients with single severe haemorrhage, and analysed the impact of surgical timing, radiological characteristics and other clinical characteristics in this consecutive series, which is the largest series of SCCMs focusing on surgical timing in the literature to date.

METHODS

Patients

The China-International Neuroscience Institute spinal vascular malformation database is an ongoing prospectively maintained

database including data from consecutive patients with spinal vascular malformations from three referral centres.[9–11] Patients diagnosed with SCCMs who were surgically treated between January 2002 and December 2021 were selected and retrospectively reviewed from this database.

Data collection

All the medical information of these patients from our online database was reviewed. We used a five-type clinical presentation classification system proposed in our previous study that is based on the four types described in the Ogilvy classification.[9 12 13] The Modified McCormick Scale (MMS) was used to evaluate neurological and disability status; scores were obtained on admission, postoperatively and during long-term follow-up.[14] Long-term follow-up was defined as the last follow-up occurring at least 6 months after surgery. In this study, we defined neurological improvement, neither improvement nor

Table 1 Baseline and clinical characteristics of 279 patients of SCCMs with at least 6 months' follow-up after surgical treatment

Characteristics	Overall	Time to surgery		P value
		≤6 weeks	> 6 weeks	
No of patients	279	70 (25.1)	209 (74.9)	
Female (%)	125 (44.8)	31 (44.3)	94 (45.0)	0.920
Mean age±SD (years)	37.2±15.2	35.4±16.3	37.8±14.8	0.241
Children (%)	32 (11.5)	13 (18.6)	19 (9.09)	0.031
Spinal level of CMs (%)				0.441
Cervical	86 (30.8)	19 (27.1)	67 (32.1)	
Thoracolumbar	193 (69.2)	51 (72.9)	142 (67.9)	
Locations in the horizontal plane (%)				0.985
Ventral	79 (28.4)	20 (29.0)	59 (28.2)	
Central	100 (36.0)	25 (36.2)	75 (35.9)	
Dorsal	99 (35.6)	24 (34.8)	75 (35.9)	
Type of symptoms (modified Ogilvy grade), n (%)				0.000
I (discrete, acute)	71 (25.4)	8 (11.4)	63 (30.1)	
II (acute, rapid)	65 (23.3)	3 (48.6)	31 (14.8)	
III (acute, gradual)	32 (11.5)	10 (14.3)	22 (10.5)	
IV (acute, mild)	90 (32.3)	18 (25.7)	72 (34.5)	
V (slow, progressive)	21 (7.5)	0 (0)	21 (10.1)	
MMS scale on admission (%)				0.000
1	35 (12.5)	8 (11.4)	27 (12.9)	
2	153 (54.8)	19 (27.1)	134 (64.1)	
3	28 (10.0)	14 (20.0)	14 (6.7)	
4	27 (9.7)	9 (12.9)	18 (8.6)	
5	36 (12.9)	20 (28.6)	16 (7.7)	
Initial MRI appearance (%)				0.053
Zabramski type I	182 (65.2)	54 (77.1)	128 (61.2)	
Zabramski type II	59 (21.2)	10 (14.3)	49 (23.4)	
Zabramski type III	38 (13.6)	6 (8.6)	32 (15.3)	
Overt haemorrhage as initial presentation (%)	224 (80.3)	63 (90.0)	161 (77.0)	0.018
Lesion size (%)				0.811
<10.0 mm	168 (60.2)	43 (61.4)	125 (59.8)	
≥10.0 mm	111 (39.8)	27 (38.6)	84 (40.2)	
Complete resection (%)	275 (98.6)	70(100)	205 (98.1)	0.244
Multiple lesions (%)	25 (9.0)	5 (7.1)	20 (9.6)	0.538

CM, cavernous malformation; MMS, modified McCormick Scale; SCCM, spinal cord cavernous malformation.;

Table 2 Long-term outcomes of patients with an MMS score of 2–5

Characteristics	Improved (%)	Stable or worsen (%)	Univariable analysis		Multivariable analysis	
			Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Sex						
Female	46 (41.8)	63 (47.0)	Reference		Reference	
Male	64 (58.2)	71 (53.0)	1.235 (0.742 to 2.053)	0.417	1.181 (0.640 to 2.180)	0.594
Age						
Children	15 (13.6)	12 (9.0)	Reference		Reference	
Adults	95 (86.4)	122 (91.0)	0.623 (0.278 to 1.393)	0.249	0.756 (0.290 to 1.970)	0.567
Lesion locations						
Cervical	25 (22.7)	42 (31.3)	Reference		Reference	
Thoracic or lumbar	85 (77.3)	92 (68.7)	1.552 (0.872 to 2.762)	0.135	0.869 (0.431 to 1.754)	0.695
Locations in the horizontal plane						
Ventral	25 (22.9)	46 (34.3)	0.569 (0.322 to 1.008)	0.053	0.447 (0.205 to 0.975)	0.043
Central	42 (38.5)	44 (32.8)	1.282 (0.756 to 2.174)	0.356	0.935 (0.458 to 1.912)	0.854
Dorsal	42 (38.5)	44 (32.8)	Reference		Reference	
Baseline neurological impairment						
Mild (MMS scale 2)	41 (37.3)	112 (83.6)	Reference		Reference	
Severe (MMS scale 3–5)	69 (62.7)	22 (16.4)	8.568 (4.709 to 15.589)	0.000	7.593 (3.811 to 15.128)	0.000
Lesion size						
< 10.0 mm	71 (64.6)	73 (54.5)	Reference		Reference	
≥10.0 mm	39 (35.5)	61 (45.5)	0.657 (0.392 to 1.103)	0.112	0.544 (0.286 to 1.034)	0.063
Surgical timing from onset						
≤ 6 weeks	47 (42.7)	15 (11.2)	5.919 (3.069 to 11.412)	0.000	3.216 (1.506 to 6.869)	0.003
>6 weeks	63 (57.3)	119 (88.8)	Reference		Reference	
No of lesions						
Single	102 (92.7)	122 (91.0)	Reference		Reference	
Multiple	8 (7.3)	12 (9.0)	0.797 (0.314 to 2.026)	0.634	0.494 (0.144 to 1.696)	0.263

MMS, Modified McCormick Scale.

worsening (stable) or worsening, by the changes in these scores. Severe neurological impairment was defined as an MMS score of 3–5.

Definition of haemorrhage and time to surgery

We defined overt haemorrhage events according to the standards from the Angioma Alliance Scientific Advisory Board as a clinical event involving both (1) acute or gradual onset symptoms referable to the anatomic location of the CMs and (2) radiological, pathological, surgical or rarely only cerebrospinal fluid evidence of recent extralesional or intralesional haemorrhage.[15] Patients with overt haemorrhage and severe impairment (MMS score of 3–5) were defined as having severe haemorrhage. The timing of the clinical course was calculated as the period between the first onset of symptoms to the surgical operation. For patients with single severe haemorrhage, we also calculated the time from severe haemorrhage to surgical operation.

Surgical technique

All operations were performed by experienced neurosurgeons from the three referral centres. Intraoperative somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) were monitored during the surgery. Especially for small and/or deep lesions, intraoperative ultrasound imaging was used to locate the lesion and ensure total resection.

Statistical analysis

We used the Fisher's exact test or Pearson χ^2 test for categorical variables and Student's t-test for continuous variables. Univariate and multivariate analyses of factors predicting neurological outcomes were performed through logistic regression with distinct outcomes (improved vs stable or worse) as dependent variables. Analyses were performed using SPSS software (V.25, IBM). All p values are two sided, and we defined statistical significance as $p<0.05$.

Table 3 Preoperative factors of patients with single severe haemorrhage

Characteristics	Overall	Time to surgery		P value
		≤6 weeks	> 6 weeks	
No of patients	69	40	29	
Female (%)	30 (43.5)	19 (47.5)	11 (37.9)	0.429
Children (%)	9 (13.0)	5 (12.5)	4 (13.8)	0.875
Spinal level of CMs (%)				0.188
Cervical	6 (8.7)	5 (12.5)	1 (3.5)	
Thoracolumbar	63 (91.3)	35 (87.5)	28 (96.6)	
Locations in the horizontal plane (%)				0.310
Ventral	20 (29.0)	9 (22.5)	11 (37.9)	
Central	27 (39.1)	16 (40.0)	11 (37.9)	
Dorsal	22 (31.9)	15 (37.5)	7 (24.1)	
MMS scale on admission (%)				0.087
3	19 (27.5)	13 (32.5)	6 (20.7)	
4	19 (27.5)	7 (17.5)	12 (41.4)	
5	31 (44.9)	20 (50.0)	11 (37.9)	
Lesion size (%)				0.964
<10.0 mm	45 (65.2)	26 (65.0)	19 (65.5)	
≥10.0 mm	24 (34.8)	14 (35.0)	10 (34.5)	
Multiple lesions (%)	9 (13.0)	4 (10.0)	5 (17.2)	0.378

CM, cavernous malformation; MMS, Modified McCormick Scale.

RESULTS

Baseline and clinical characteristics

A total of 349 patients with a diagnosis of SCCMs confirmed by pathological findings who underwent surgery between January 2002 and December 2021 were included. Of these, 70 were excluded from further analysis because of incomplete data or loss to follow-up. A total of 279 patients were ultimately included.

The baseline and clinical characteristics were stratified by the period from first onset of symptoms to surgical treatment (table 1). Patient ages ranged from 3 to 70 at the time of admission. The mean time from initial symptomatic onset to operation was 14.8±29.3 months. Seventy (25.1%) patients underwent surgery during the acute stage (≤6 weeks). Children and patients with overt haemorrhage and acute and severe clinical presentation tended to accept early surgery. Complete resection was achieved in 275 (98.6%). Four patients experienced subtotal resection due to the presence of a blurred boundary between the diffused lesions and the adjacent tissues, making complete resection unsafe.

Long-term outcome of all surgical treated patients

Two hundred and seventy-nine patients were followed up for at least 6 months. The mean clinical follow-up duration was 31.8±28.0 months. Compared with MMS on admission, the long-term outcome results demonstrated that 110 (39.4%) patients improved, 159 (57.0%) were stable and 10 (3.6%) worsened. The mean MMS score was 2.56±1.21 at admission and 2.04±0.99 at the last follow-up. Four patients (1.4%) accepted operation after 6 weeks and experienced recurrence of the lesions during the follow-up.

For patients with MMS scores of 1, there is no dynamic range in the MMS to show improvements; therefore, we discuss this situation separately and classify outcomes as stable or worse. Although we found no significant factors that contributed to unfavourable outcomes, 7 (20%) patients with an MMS score of 1 at baseline worsened at the last follow-up, which represents a significantly higher proportion than other patients (χ^2=31.2, p<0.001). For patients with an MMS score of 2–5, univariate and multivariate analyses were used to identify the factors that influenced the long-term outcome (table 2). In the univariate and multivariate analyses, a surgical timing of ≤6 weeks from onset (adjusted OR 3.211, 95% CI 1.504 to 6.856, p=0.003) and severe impairment (adjusted OR 7.548, 95% CI 3.786 to 15.050, p<0.001) were significant predictors of improved MMS. The results also indicated that patients with ventrally located lesions showed worse outcomes (adjusted OR 0.449, 95% CI 0.206 to 0.981, p=0.045).

Additionally, although no significant difference was found, all four patients who experienced incomplete resection and the four cases of recurrence underwent surgery more than 6 weeks after the onset of symptoms, with a minimum disease duration of 2 months.

Table 4 Long-term outcomes of patients with single severe haemorrhage

Characteristics	Improved (%)	Stable or worsen (%)	Univariable analysis		Multivariable analysis	
			Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Sex						
Female	22 (42.3)	8 (47.1)	Reference		Reference	
Male	30 (57.7)	9 (52.9)	1.212 (0.404 to 3.641)	0.732	1.778 (0.432 to 7.323)	0.426
Age						
Children	6 (11.5)	3 (17.7)	Reference		Reference	
Adults	46 (88.5)	14 (82.4)	1.643 (0.363 to 7.433)	0.519	1.848 (0.299 to 11.426)	0.509
Lesion locations						
Cervical	5 (9.6)	1 (5.9)	Reference		Reference	
Thoracic or lumbar	47 (90.4)	16 (94.1)	0.588 (0.064 to 5.413)	0.639	2.289 (0.112 to 46.677)	0.590
Locations in the horizontal plane						
Ventral	12 (23.1)	8 (47.1)	0.338 (0.107 to 1.066)	0.064	0.153 (0.020 to 1.151)	0.068
Central	20 (38.5)	7 (41.2)	0.893 (0.293 to 2.725)	0.842	0.453 (0.061 to 3.379)	0.440
Dorsal	20 (38.5)	2 (11.8)	Reference		Reference	
MMS on admission						
3	17 (32.7)	2 (11.8)	Reference		Reference	
4	16 (30.8)	3 (17.7)	2.074 (0.522 to 8.236)	0.300	0.913 (0.087 to 9.544)	0.939
5	19 (36.5)	12 (70.6)	0.240 (0.073 to 0.786)	0.018	0.124 (0.014 to 1.140)	0.065
Lesion size						
< 10.0 mm	35 (67.3)	10 (58.8)	Reference		Reference	
≥10.0 mm	17 (32.7)	7 (41.2)	0.694 (0.225 to 2.140)	0.525	0.570 (0.131 to 2.482)	0.454
Surgical timing from onset						
≤ 6 weeks	34 (65.4)	6 (35.3)	3.463 (1.100 to 10.905)	0.034	4.901 (1.126 to 21.325)	0.034
>6 weeks	18 (34.6)	11 (64.7)	Reference		Reference	
No of lesions						
Single	46 (88.5)	14 (82.4)	Reference		Reference	
Multiple	6 (11.5)	3 (17.7)	0.609 (0.135 to 2.754)	0.519	1.770 (0.228 to 13.712)	0.585

MMS, Modified McCormick Scale; .

Patients with single severe haemorrhage

Among 69 patients with single severe haemorrhage, 40 (58.0%) underwent surgery within 6 weeks. Preoperative factors of these patients with or without undergoing surgery within 6 weeks from severe haemorrhage are shown in table 3. No significant differences were found in baseline characteristics. Fifty-two (75.3%) of them had an improved outcome at the last follow-up. The mean period from the onset of severe haemorrhage to surgery was 58.8±74.2 days, and the median period was 39 days.

In the univariate analysis, whether the time to surgery was within 6 weeks from severe haemorrhage (p=0.029) and the MMS score on admission (p=0.046) had a significant influence on the improvement of MMS score at the last follow-up. In the multivariate analysis, undergoing early surgery (≤6 weeks from the onset of severe haemorrhage) improved the final outcome (adjusted OR 4.901, 95% CI 1.126 to 21.325, p=0.034; table 4).

For surgeries performed during the hyperacute phase (≤2 weeks), compared with those performed delayed in the acute stage (2–6 weeks), there was an advantage in the rate of improved outcomes (90.91% vs 82.76%). Especially for paraplegic or quadriplegic patients (MMS=5), 7 patients underwent surgery during the hyperacute phase and 13 patients were treated later within the acute stage; a higher rate of favourable outcome (MMS=1–2 at the last follow-up) was found in the former group (57.1% vs 23.1%). However, no significant difference was found for patients with a single severe haemorrhage outcomes in whether the operation was performed during the hyperacute phase due to the limitation of the sample size.

DISCUSSION

There is still no consensus on the timing of surgical treatment for SCCMs. Most previous studies are limited by small sample sizes. To the best of our knowledge, this

is the largest series of SCCM patients with data on long-term outcomes focusing on surgical timing to date. We analysed data from all 279 surgically treated patients. We found that patients with significant symptoms (MMS=2–5) could benefit from early surgery (≤6 weeks), especially for those with severe neurological impairment.

In regard to patients with slight symptoms (MMS=1), in view of the higher rate of deterioration in this group, conservative treatment could be considered. However, even in patients with no previous haemorrhage, the 2-year cumulative risk of haemorrhage was 4.6%.[9] When haemorrhage or neurological decline occurs, early surgical intervention should be performed for better outcomes.

We also focused on 69 patients with severe haemorrhage. In clinical practice, we often find that some patients with SCCMs, even those with long-term mild symptoms, could have severe haemorrhage with acute decline in neurological function. Whether and when to treat these patients remains controversial and is one of the key questions in treating SCCMs. Therefore, we counted the time to surgery of these patients from their acute onset of severe haemorrhage and analysed them as a separate group. Among these participants, there was a higher rate of improvement for patients who underwent surgery within 6 weeks of their severe haemorrhage.

Similarly, for patients with severe haemorrhage, there is the question of whether surgeries should be performed during the hyperacute phase (≤2 weeks). Jallo *et al* suggested that delaying surgery for several weeks may facilitate resection after acute haemorrhage.[16] Some studies also proposed performing the operation later. After 4–6 weeks from bleeding, the hematoma resolves, glial scar development can protect the normal spinal cord, and the border between the lesion and normal tissue is clear, which benefits gross resection.[17 18] However, Duan *et al* found that emergency rescue surgery within 3–7 days after acute onset can improve the outcome of deteriorative patients.[19] In our study, compared with surgery performed delayed in 3–6 weeks, we found a higher rate of improvement in patients with severe haemorrhage and more benefit for paraplegic or quadriplegic patients in cases accepting surgery within 2 weeks. Although this finding may be limited by the number of cases and no significant difference was found, it seems to be a safe and effective treatment strategy. We will continue to consider these patients in future studies.

Influence of surgical technique

Surgical technique can also influence the outcome. Myelotomy and lesion excision for intramedullary occupation can also cause a decline in neural function.[13] Surgery in the very early stage is more difficult because of the severe oedema and solid nature of the haematoma. Therefore, it is challenging for neurosurgeons to perform operations early. Intralesional decompression is important to dissect the unclear boundary between the haemorrhagic lesion and edematous spinal cord tissue. It is also vital to choose an appropriate approach for lesions in different horizontal planes. Ventral or deep lesions are considered to lead to poorer functional results. We proposed a new surgical approach, anterior to dorsal root entry zone myelotomy (ADREZotomy), for the removal of cervical and thoracic ventrolateral deep SCCMs due to its safety and feasibility.[20] Intraoperative assistive technologies such as SSEPs, MEPs and intraoperative ultrasound imaging can also help with safe resection. For those centres without necessary equipment or neurosurgeons specialised in intramedullary disease, early referral should be considered.

Limitation

This study was retrospectively designed. Because of the poor natural history of SCCMs and good prognosis of surgery, this topic is not suitable for prospective randomised controlled studies. Restricted by the time of referral and the understanding of this disease in local hospitals, the number of patients in the hyperacute stage was limited. In this study, we judged outcomes qualitatively, and it is possible that the degree of outcome improvement differs in different stages. As stated above, surgical technique and intraoperative assistive technologies can also influence outcomes. The included patients were treated at three different referral centres and by different surgeons, which may cause potential selection and outcome biases.

CONCLUSION

The timing of surgery can influence the long-term outcomes of patients with SCCMs. For symptomatic SCCMs, especially in patients with severe haemorrhage, surgery performed within 6 weeks yielded better outcomes. Early diagnosis and surgery or referral should be considered as an effective treatment strategy.

Contributors HZ, LS, TH and FL: These authors identified the correlation between the disease and the timing of surgery through their clinical practice. They contributed a large amount of data, provided guidance in the establishment and improvement of the database. They also guided the writing of this manuscript. Moreover, they critically revised and reviewed the article. HZ and LS, as guarantors, were responsible for the overall content. AT, ZC and JR: They established and maintained the database, which was instrumental in obtaining the data for this study. They conducted follow-ups, data analysis, identified statistical conclusions, and contributed to the writing of the manuscript. They contributed equally to this work and should be considered cofirst authors. YR, MY, GL, CH, XL, GZ, PH, YM, JY, JL, LB and FY: As mentioned above, the disease addressed in this paper is relatively rare. These authors belong to different centres and collectively contributed to the acquisition of surgical-related data from the database mentioned in the manuscript. QL: As experts in the field of radiology, she assisted in collecting imaging data from the database and provided guidance in the interpretation of the images. HZ and LS, as guarantors, were responsible for the overall content. AT, ZC and JR: They established and maintained the database, which was instrumental in obtaining the data for this study. They conducted follow-ups, data analysis, identified statistical conclusions, and contributed to the writing of the manuscript. They contributed equally to this work and should be considered cofirst authors. YR, MY, GL, CH, XL, GZ, PH, YM, JY, JL, LB and FY: As mentioned above, the disease addressed in this paper is relatively rare. These authors belong to different centres and collectively contributed to the acquisition of surgical-related data from the database mentioned in the manuscript. QL: As experts in the field of radiology, she assisted in collecting imaging data from the database and provided guidance in the interpretation of the images.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Committee of Xuanwu Hospital,Capital Medical University. Participants gave informed consent to participate in the study before taking part.

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