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Investigation of Effective Factors on the Estimated Hemorrhage Intraoperative In Brain Meningioma Surgery in Rasoul-E-Akram Hospital

Running Title: Imaging factors and the volume of hemorrhage

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Highlights

- The size of mass was positively associated with estimated blood loss volume in meningioma surgery.
- The mean time of operation was strongly correlated with the rate of bleeding in meningioma surgery.
- The closer tumor to the sinuses the more blood volume will be loss during operation in meningioma surgery.
- The rate of bleeding was more expected in hypertensive patients in meningioma surgery.

Plain Language Summary

Meningioma is the most common tumor in the central nervous system. The primary and definitive diagnosis of meningitis is based on histological evaluation. The use of imaging techniques such as Magnetic Resonance Imaging (MRI) can be helpful in preoperative diagnostic evaluations in patients who are candidates for surgical management of meningioma. These modalities can provide good diagnostic performance to predict the operational risk as well as the likelihood of procedural complications such as brain hemorrhage. In this study, eligible patients were those who suffered from meningioma, completely eliminated the lesion and preoperative diagnostic method was MRI. Demographic characteristics of the patients including age, gender, preoperative laboratory examinations, history of cardiovascular disease, diabetes and history of anti-platelet use, operation time and total intraoperative blood loss were recorded. The tumor volume was measured and calculated in coronal, axial and sagittal cuts in MRI images, as well as measured parameters such as maximum connection to dura, tumor size and distance to the nearest sinuses. Brain edema was determined as mild, moderate and severe according to its volume in relation to

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tumor volume (less, equal and more in size respectively). The results showed that there was no association between the rate of hemorrhage and gender, age, history of diabetes, history of coronary disease, history of anti-thrombocyte tumor size, but the duration of surgery, history of hypertension and distance to the nearest sinuses were the main determinants for the severity of hemorrhage in meningioma surgery.

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ABSTRACT

Purpose: Although the primary and definitive diagnosis of meningioma is based on histological assessment, the use of imaging methods such as Magnetic Resonance Imaging (MRI) is very helpful to describe lesion's characteristics. Accordingly, we decided to study the effect of imaging factors such as MRI on the volume of hemorrhage (estimated blood loss) during meningioma surgery**.**

Methods: In this study, which was performed as a cross-sectional retrospective analytical study, the eligible patients were those who suffered meningioma and were candidate for surgery. A total of 40 patients with meningioma were selected and reviewed. The findings of the preoperative imaging were recorded and then estimated blood loss during the surgery was determined.

Results: A reverse association was revealed between the degree of proximity to nearest sinus and the rate of bleeding. Also, the size of mass was positively associated with the rate of bleeding, but there was no significant correlation between the volume of bleeding and other parameters including degree of edema, volume of mass, the site of tumor in brain, and histological subtype of the tumor. The mean time of operation was strongly correlated with blood loss. The rate of bleeding was more expected in hypertensive versus normotensive patients.

Conclusion: As a final conclusion, bleeding in various volumes can be a common finding in intracranial meningioma surgery. In total, tumor size, duration of surgery, history of hypertension and distance to nearest sinuses were the main determinants for the severity of hemorrhage in meningioma surgery.

Keywords: Hemorrhage, Meningioma, Magnetic resonance imaging, Diagnosis

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Introduction

Meningioma is the most common tumor in the central nervous system, which accounts for between 16% and 20% of the total intracranial tumors (Toh et al.,2008). Magnetic Resonance Imaging (MRI) technique is a selective modality for assessing meningioma that not only shows the tumor's position with high contrast but also is able to evaluate intra and extera axial lesions (Whittle, Smith, Navoo & Collie, 2004; O'Leary, Adams, Parrish & Mukonoweshuro, 2007; Nagar et al., 2008; Buetow, Buetow & Smirniotopoulos;1991). In addition to MRI, Computed Tomography (CT) scan also plays an important role in detecting calcification as well as lesions associated with calvarium changes (Tokgoz et al., 2005). However, typical meningioma has well-known visual characteristics; there are also various atypical and unusual types that in addition to creating a diagnostic challenge for meningioma, they have also questioned the diagnostic accuracy of imaging techniques (Paek et al., 2005; Hakyemez et al., 2006). It is very important for a radiologist to find a complete understanding of the atypical features of the disease in the images provided to get the correct diagnosis (Elder, Atkinson, Zee & Chen, 2007; Komotar, Keswani, Wityk, 2003).

In MRI, meningioma appears in the form of signal strength characteristics, including isointensity to mild hyperintensity, relative to gray matter, on the T2 sequence (Heye, Maleux, Van Loon & Wilms, 2006). After applying contrast, meningioma appeared in the form of homogenous enhancement (Yue et al., 2008). However, the lesions occasionally exhibited necrosis or calcification, which in this case lacked enhancement. Calcification is visualized better in the CT scan view (Chen et al., 2004). On MRI view, especially on T2 sequences, calcification can be detected in the form of low intensity signals (Bitzer et al., 1998). Contrast is also well-suited for detecting plaque-shaped meningioma, which is appeared as asymmetrical thickness on dura (Nakano, Nakano, Miura, Itoh & Suzuki, 2002).

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Although the primary and definitive diagnosis of meningioma is based on histological assessment, the use of imaging methods such as MRI has found a special place in this field today that not only detects the nature of the tumor but also helps detect local invasion, especially on T2-weighted images. Therefore, with regard to non-invasive nature, imaging techniques can be helpful in preoperative diagnostic evaluations in patients who are candidates for surgical management of meningioma. These modalities can provide good diagnostic performance to predict the operation risk as well as the likelihood of procedural complications such as brain hemorrhage. Accordingly, we decided to study the effect of imaging factors such as MRI on the rate of hemorrhage during meningioma surgery**.**

Materials And Methods

In this observation study, which was performed as a cross-sectional retrospective analytical study, the eligible patients were those who suffered meningioma and the lesion totally removed. Exclusion criteria also were contraindications for imaging with different methods such as MRI and those patients with significant bony involvement by tumor. A total of 40 patients with meningioma admitted to Rasoul-e-Akram Hospital in Tehran from 2015 and 2016 were selected and reviewed.

Demographic characteristics of the patients including age, sex, preoperative laboratory examinations, history of cardiovascular disease, diabetes and history of anti-platelets use were collected from patient's medical records. The operation time and total intraoperative blood loss were recorded from patient's anesthesia file. The most common manifestation in the outcome analysis were headache, followed by blurred vision, and limb weakness.

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preoperative, data of the brain were received from MRI images. MRI examinations were taken on a 1.5 T scanner (Philips Medical Systems,ingenia). Imaging protocols in the T1 sequence were performed with contrast**.** Slice –thickness was 2 mm.

The location of the tumors was classified as parasagittal, parafalx , convexity, skull base (anterior, posterior, middle).

The tumor volume was measured and calculated using the ellipsoid formula, $\frac{a \times b \times c}{2}$.

a) the largest diameter of the tumor in the axial view ; b) the diameter of the tumor in the same cut of the axial view perpendicular to a; and c) the height of the tumor using the number of cut counts that the tumor is observed in. also parameters such as maximum connection to dura, tumor size and distance to nearest sinuses was measured.

The size of the tumor represents the diameter of the tumor. The axial, coronal, and sagittal views are examined and the largest diameter of the tumor is specified in each of them.

Brain edema was determined as mild, moderate and severe according to its volume in relation to tumor volume (less, equal and more in size respectively).

The findings of the preoperative imaging were recorded and then volume blood loss has been evaluated during surgery. The frequency of hemorrhage cases was finally determined based on imaging findings.

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of the data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of the cells with expected count of less than 5 were observed. The quantitative variables were also compared with t test or Mann- Whitney U test. The correlation between the quantitative parameters was examined by the Pearson's correlation

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test. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

Totally 40 patients with meningioma who underwent total surgical removal were assessed, the mean age of patients was 54.90 ± 12.66 years ranged 28 to 77 years and 72.5% were female. Regarding cardiovascular risk factors, 30.0% were hypertensive, 12.5% were diabetic, 7.5% had history of coronary disease and 7.5% had history of anti-platelets use. The most common manifestation was headache (67.5%), followed by blurred vision (30.0%), and limb weakness (25.0%). In assessment by imaging, mild, moderate and severe brain edema was revealed in 45.0%, 37.5% and 17.5% respectively. Regarding site of tumor, 25.0% was located in convexity, 45.0% in skull base (72.2% in anterior and 27.7% in posterior sites), and 30.0% in parasagittal. The mean size of meningioma was 41.72 ± 19.42mm with the mean volume of 49.36 ± 61.90mm3 (Table 1). Regarding subtypes of meningioma, meningothelial type was detected in 35.0%, transitional in 30.0%, atypical in 10.0%, cystic meningioma in 5.0%, non-specified Grade 1 in 5.0%, angiomatosis in 5.0%, psammomatous in 2.5% and microcystic in 5.0%. The volume of hemorrhage was 925.64 ± 756.19mL and the mean operation time was 7.15 ± 2.03hours. With regard to tumor distance to the nearest sinus, the proximity was found 50.0%, 15% and 35% for superior sagittal, transverse and cavernous sinuses respectively.

A reverse association was revealed between the degree of proximity and the volume of bleeding (p = 0.06).

Also, the size of mass was positively associated with estimated blood loss volume (p = 0.003), but there was no significant correlation between the volume of bleeding and other parameters including degree of edema, volume of mass, the site of tumor in brain, type of

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tumor and maximum connection to dura (Table 2). The mean time of operation was strongly correlated with the rate of bleeding. ($p = 0.001$). We showed also no association between rate of hemorrhage and gender, age, history of diabetes, history of coronary disease, history of anti-platelet use, and the mean level of serum hemoglobin and WBC and platelet counts. But, the rate of bleeding was more expected in hypertensive versus normotensive patients (Table 3).

Discussion

Hemorrhage following brain tumor surgery has a negative effect on the outcome of treatment of such tumors. In this regard, the volume of massive hemorrhage and the high need for transfusion during and after surgery are important predictors of adverse outcomes in the treatment of these patients. Therefore, predicting this volume of surgical bleeding not only can improve the patient's outcomes but also affect the long-term survival of patients. Hemorrhage from meningioma as well as bleeding from the surgical site are relatively common phenomena. Therefore, given its significant impact on the outcome of treatment, its prediction will be vital. Given that the non-invasive evaluation of these patients before and after surgery by imaging, especially with MRI, is essential for the evaluation of tumor progression and favorable advancement of treatment, pre-surgical MRI indexes can be used to predict the bleeding during surgery. The main goal of the project was to describe the imaging characteristics of meningioma by MRI and aided to reduce intraoperative blood loss. In this study, we found that three of the indexes related to the primary indicators of patients (history of hypertension), related to surgery (time of operation) and related to the characteristics of lesion (size of the tumor) with are closely related to the volume of the bleeding during the operation. In other words, in hypertensive patients or patients with a large size of the meningioma, as well as a longer duration of surgery can increase the likelihood of

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bleeding during surgery. There wasn't significant correlation between the volume of bleeding and tumor volume, the reason of this cannot be easily evaluated. Perhaps the largest tumor diameters are a better benchmark for showing the depth of its penetration into the brain. For example, in two tumors of equal volume, in elliptical and spherical form, in the elliptical tumor the shape of the penetration of the lesion is larger in the brain, so it will get more time to rescue it. Of course, this argument cannot be presented without a closer examination, and more studies are possible.

Therefore, all measures should be taken to prevent bleeding and transfusion during surgery in hypertensive patients as well as patients with large meningioma.

In result we can conclude the closer tumor to the sinuses the more blood volume will be loss during operation.

Very limited studies have been done on the relationship between underlying characteristics and MRI and prediction of bleeding during surgery. In the study by Lü et al (Lü, 2013), the related factors influencing bleeding severity were the origin of the tumor, tumor volume, bleeding vessel or venous sinus involvement, and the size of the tumor was consistent with our study. He also found that calcification, invasive behavior, dural tail symptoms, peripheral edema, and adjacent bone involvement did not affect hemorrhage. However, in his study, the relationship between bleeding and baseline indices such as history of hypertension was not evaluated, also in the study by Murph et al (Murphy et al., 2013), they found that preoperative MR-elastography can help determine tumor's stiffness and bleeding during meningioma surgery. Hoover and colleagues in their study mentioned that preoperative MRI had the ability to predict the tumor's stiffness and its bleeding probability in 90% of cases (Hoover, Morris & Meyer, 2011). As previously mentioned the cause of bleeding in meningeal tumors, either prematurely due to the nature of the tumor or during its therapeutic operation, can be due to the weakening of the nerve and ductile vessels, intratumoral angiogenesis, vascular

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wall invasion, blood dyscrasia, and simultaneous anticoagulation. However, the surgeon's experience should also be considered as the main cause of bleeding or its control (Lü, 2013). In other studies, the association between tumor volume and hemorrhage during surgery, especially in the T2 sequence, has been investigated. In this study, we tried to apply other imaging factors that are less studied on them. Howevere the limitations of this study are the lack of consideration of more factors in imaging in assessing the volume of bleeding. The other limitation is the low number of patients. We hope that in future these deficites will be compensate for better results.

Conclusion

As a final conclusion, bleeding in various volumes can be a common finding in intracranial meningioma surgery. In total, tumor size, duration of surgery, history of hypertension and distance to nearest sinuses were the main determinants for the severity of hemorrhage in meningioma surgery.

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Ethical Considerations

Compliance with ethical guidelines

The study was the residency thesis of Ahmad Alagha approved by the Research and Ethics Committee under the code number 1396.9211255005 at Iran University of Medical Sciences, Tehran, Iran.

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Conflict of interest

None of the authors had any conflict of interest.

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References

1. Toh CH, Castillo M, Wong AM, Wei KC, Wong HF, Ng SH, et al. (2008). Differentiation between classic and atypical meningiomas with use of diffusion tensor imaging. AJNR Am J Neuroradiology, 29(9),1630-1635. 2.

2. Whittle IR, Smith C, Navoo P, Collie D. (2004). Meningiomas. Lancet, 363(9420),1535–1543.

3. O'Leary S, Adams WM, Parrish RW, Mukonoweshuro W. (2007). Atypical imaging appearances of intracranial meningiomas. Clin Radiol, 62(1),10–17.

4. Nagar VA, Ye JR, Ng WH, Chan YH, Hui F, Lee CK, et al. (2008). Diffusion-weighted MR imaging: diagnosing atypical or malignant meningiomas and detecting tumor dedifferentiation. AJNR Am J Neuroradiol, 29(6),1147–1152.

5. Buetow MP, Buetow PC, Smirniotopoulos JG. (1991). Typical, atypical, and misleading features in meningioma. Radiographics, 11(6),1087–1106.

6. Tokgoz N, Oner YA, Kaymaz M, Ucar M, Yilmaz G, Tali TE. (2005). Primary intraosseous meningioma: CT and MRI appearance. AJNR Am J Neuroradiol, 26(8),2053–2056.

7. Paek SH, Kim SH, Chang KH, Park CK, Kim JE, Kim DG, et al. (2005). Microcystic meningiomas: radiological characteristics of 16 cases. Acta Neurochir (Wien),147(9),965–972.

8. Hakyemez B, Yildirim N, Erdoğan C, Kocaeli H, Korfali E, Parlak M. (2006). Meningiomas with conventional MRI findings resembling intraaxial tumors: can perfusion-weighted MRI be helpful in differentiation?. Neuroradiology, 48(10),695–702.

9. Elder JB, Atkinson R, Zee CS, Chen TC. (2007). Primary intraosseous meningioma. Neurosurg Focus, 23(4),1–9.

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10. Komotar RJ, Keswani SC, Wityk RJ. (2003). Meningioma presenting as stroke: report of two cases and estimation of incidence. J Neurol Neurosurg Psychiatry, 74(1),136–137.

11. Heye S, Maleux G, Van Loon J, Wilms G. (2006). Symptomatic stenosis of the cavernous portion of the internal carotid artery due to an irresectable medial sphenoid wing meningioma: treatment by endovascular stent placement. AJNR Am J Neuroradiol, 27(7),1532–1534.

12. Yue Q, Isobe T, Shibata Y, Anno I, Kawamura H, Yamamoto Y, et al. (2008). New observations concerning the interpretation of magnetic resonance spectroscopy of meningioma. Eur Radiol, 18(12),2901–2911.

13. Chen TY, Lai PH, Ho JT, Wang JS, Chen WL, Pan HB, et al. (2004). Magnetic resonance imaging and diffusion-weighted images of cystic meningioma: correlating with histopathology. Clin Imaging, 28(1),10–19.

14. Bitzer M, Opitz H, Popp J, Morgalla M, Gruber A, Heiss E, et al. (1998). Angiogenesis and brain oedema in intracranial meningiomas: influence of vascular endothelial growth factor. Acta Neurochir (Wien), 140(4),333–340.

15. Nakano T, Asano K, Miura H, Itoh S, Suzuki S. (2002). Meningiomas with brain edema: radiological characteristics on MRI and review of the literature. Clin Imaging, 26(4),243–249.

16. Lü J. (2013). Correlation between preoperative imaging features and intraoperative blood loss of meningioma: a new scoring system for predicting intraoperative blood loss. J Neurosurg Sci, 57(2),153-61.

17. Murphy MC, Huston J 3rd, Glaser KJ, Manduca A, Meyer FB, Lanzino G, et al. (2013). Preoperative assessment of meningioma stiffness using magnetic resonance elastography. J Neurosurg, 118(3):643-648.

Accepted Manuscript (Uncorrected Proof)

18. Hoover JM, Morris JM, Meyer FB. (2011). Use of preoperative magnetic resonance imaging T1 and T2 sequences to determine intraoperative meningioma consistency. Surg Neurol Int, 2,142.

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Table 1: Meningioma characteristics in MRI

Edema	
Mild	18 (45.0%)
Moderate	15 (37.5%)
Severe	7 (17.5%)
Location of tumor	
Convexity	10 (25.0%)
skull base	18 (45.0%)
Ant Skull base	13 (72.2%)
Pos Skull base	5 (27.7%)
Parasagittal	12 (30.0%)
Size of tumor	41.72 ± 19.42
Volume of tumor	49.36 ± 61.90
Maximum connection to dura	39.44 ± 21.14
Subtypes	
Meningothelial	14 (35.0%)

Transitional	12 (30.0%)
Atypical	4 (10.0%)
Cystic meningioma	2 (5.0%)
non specify Grade 1	2 (5.0%)
Angiomatosis	2 (5.0%)
psammomatous	1 (2.5%)
Microcystic	2 (5.0%)
distance from the superior Sagittal Sinus	20 (50%)
distance from the Transverse sinus	6 (15%)
distance to Cavernous sinus	14 (35%)

Table 2: Relationship between bleeding volume and imaging indices

Index	Mean or R coefficient	P value
Edema		0.456
Mild	861.11 ± 688.25	
Moderate	893.33 ± 797.95	
Severe	1340.00 ± 952.89	
Tumor site		0.376
Convexity	1080.00 ± 868.65	
skull base	1025.00 ± 872.83	
Parasagittal	585.00 ± 212.20	
Mean size	0.463	0.003
Mean volume	0.223	0.171
Maximum connection to dura	0.279	0.085
Subtypes		0.995
meningothelial	1037.50 ± 1154.11	
Transitional	1087.50 ± 972.37	
Atypical	737.50 ± 325.00	
Cystic	850.00 ± 212.13	

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non specify G1	750.00 ± 212.13	
Aniomathosis	725.00 ± 106.07	
Psammomatos	0.350	
Microsytic	0.800	
Operation time	0.710	0.001
Distance to sinus	-0.084	0.06

Table 3: Relationship between bleeding volume and baseline indices of patients

Index	Mean or R coefficient	P value
Gender		0.903
Male	934.48 ± 752.51	
Female	900.00 ± 807.26	
Age	0.217	0.186
Hypertension		0.044
Yes	1283.33 ± 930.38	
No	750.00 ± 625.93	
Diabetes		0.543
Yes	730.00 ± 723.36	
No	954.42 ± 767.06	
Coronary disease		0.109
Yes	1600.00 ± 1352.77	
No	869.44 ± 688.51	
Anti-platelet use		0.338
Yes	1333.33 ± 1457.17	
No	891.67 ± 695.75	
Hemoglobin level	0.170	0.307
WBC count	0.124	0.458
Platelet count	0.009	0.958

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