Nimodipine reduces delayed cerebral vasospasm after intracranial tumor surgery: a retrospective study

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Abstract

Background Cerebral vasospasm (CVS) is a serious neurosurgical complication. This retrospective study was performed to analyze if nimodipine can improve prognosis and reduces ischemia secondary to delayed CVS after intracranial tumor surgery.

Methods Retrospective analysis of 94 patients with an anterior cranial fossa tumor and underwent intracranial tumor surgery was performed, with 42 cases treated with normal saline and 52 cases treated with nimodipine solution. Transcranial Doppler ultrasonography was used to measure velocity in the middle cerebral artery (MCA) and the distal extracranial internal carotid artery (eICA). An examination was conducted 1 day before surgery and 1, 3, 5, 7, and 14 days after surgery. Follow-up was performed using the Glasgow Outcome Scale (GOS) 3 months after discharge.

Results We showed that in the nimodipine group, CVS occurred in 13 (25%) patients who did not have CVS in the first three days after operation; nine patients had CVS between 4 and 7 days, and 4 had CVS between 8 and 14 days. In the normal saline group, nineteen (45%) patients had CVS, 3 presented with CVS within 3 days, 11 between 4-7 days and 5 between 8-14 days. A significant difference in the occurrence of CVS was observed between the two groups. Preoperative and postoperative the MCA velocities were compared, revealing a significant change in the normal saline group ($P < 0.05$) but not in the nimodipine group. Furthermore, significant differences in the outcome were observed between the two groups at the 3-month follow-up ($P < 0.05$).

Conclusions Nimodipine markedly improves prognosis and significantly reduces ischemia secondary to delayed CVS after intracranial tumor surgery, as well as the risks of mortality and morbidity.

Introduction

Cerebral vasospasm (CVS) is a serious neurosurgical complication[1, 2]. Currently, studies are focused on CVS induced by subarachnoid hemorrhage (SAH) caused by arterial aneurysm and traumatic SAH[3, 4].

There are a few cases that have been reported regarding delayed CVS after intracranial tumor surgery.[5-7]. The intracranial low-density zone visualized with CT caused by CVS is usually misdiagnosed as surgical injury or postoperative brain edema, leading to incorrect treatment of patients and a poorer prognosis. It has been shown that the incidence of CVS after intracranial tumor surgery is relatively high (22-49%), especially if an immediate diagnosis and/or treatment is delayed, consequently decreasing the effectiveness of surgery[8, 9].

Nimodipine is a second-generation dihydropyridine class calcium antagonist, and nimodipine has high lipophilicity, which makes it rapidly cross the blood-brain barrier. The main mechanism of nimodipine is selective blockade of intracellular calcium flow through L-type calcium channels[10]. Nimodipine is considered the first choice for the prevention of CVS after SAH and has been approved in the United States[11], Canada[12] and other countries[13]. Prophylactic use of nimodipine during craniotomy is effective in the prevention of neurological dysfunction after surgery[14].

This study retrospectively analyzed the 5-year clinical data of 94 patients with an anterior cranial fossa tumor treated with normal saline and treated with nimodipine solution. Here, we report the effects of nimodipine on CVS after intracranial tumor surgery.

Material And Methods

This study was reviewed and approved by the Ethics Committee of the first hospital of Jilin University. All patients provided informed consent. Patients with an anterior cranial fossa tumor who were treated in our hospital from January 2011 to May 2012 were included in this study. The inclusion criteria were as follows: confirmed diagnosis of an anterior cranial fossa tumor; consent to undergo intracranial tumor surgery; the performance of the relevant research; and no serious dysfunction of the heart, lung, liver or kidney. The exclusion criteria were as follows: severe coagulopathy, hypertension, atherosclerosis, diabetes, postoperative bleeding after intracranial tumor craniotomy, malignant cerebral edema, or a reopening of the craniotomy site. All patients were followed up for at least 3 months.

A total of 94 patients were included in the study. Fifty patients were male, and forty-four were female. Patients ranged in age from 17 to 80 years, and the average age of these patients was 49.6 years. In the nimodipine group, there were 27 males and 25 females, while in the normal saline group, there were 23 males and 19 females. Patients ranged in age from 17-80 years. The average age in the nimodipine group and the normal saline group was 48.9 and 49.8 years, respectively. No significant difference in sex or age was observed between the two groups of patients. The pathological diagnoses included meningioma (n=65), glioma (n=18), brain metastases (n=10) and schwannoma (n=1).

Grouping

Surgery was performed under general anesthesia, and microsurgical techniques were applied to avoid stretching the brain tissue and blood vessels as little as possible. All patients performed surgery by subfrontal approach, enlarged subfrontal approach, or pterional approach. Careful hemostasis was performed if hemorrhaging occurred during surgery. All patients did not use any vasoactive agent a week before surgery.

Patients were randomly divided into two groups based on whether they were treated with nimodipine: 1. The nimodipine group (n=52) received nimodipine (Bayer, Germany) solution (10 mg/50 mL, during surgery and for 7 days after surgery) and tablets (30 mg/per tablet; from the 8th day to the 14th day after surgery). All intracranial tumors were totally resected under a microscope. Varying degrees of vascular invasion were observed among all patients, especially in sellar tumors. The surgical field was soaked in diluted nimodipine solution (stock: normal saline=1:5) for 10 minutes—including the exposed nerve and blood vessel, especially the optic nerve and the MCA. In sellar region procedures, the optic nerve and middle cerebral artery (MCA) were exposed (Fig. 1A), and nimodipine lavage of the optic nerve and MCA was administered (Fig. 1B). After surgery, the patients were continuously perfused with nimodipine at an initial dose of 0.5 mg/h via a microinfusion pump (Zhejiang University Medical Instrumental Co. Ltd; Type WZ-50C2); then, the dose was gradually increased to 2 mg/h if the patient tolerated the treatment

without hypotension and was continuously infused for 7 days. After soaking, the optic nerve and MCA were viewed in different colors: the MCA was viewed as purple-red, and the optic nerve was viewed as yellowish-white. Next, patients were given oral nimodipine tablets (60 mg/4 h) for 7 days. 2. The normal saline group (n=42): the surgical field was soaked in normal saline for 10 minutes. In addition to the continued use of nimodipine after surgery in the nimodipine group, the normal saline followed by the same treatment dose and schedule as the nimodipine group after surgery.

Patients in both groups also received standard care, including, lowering of intracranial pressure, hemostasis, and prevention of infection.

Modified Fisher Scale

Brain computed tomography (CT) was performed on the day of surgery. Classification of the amount and distribution of SAH was based on the modified Fisher scale[15]. Grade 0: No SAH or no intraventricular blood; Grade I: Thin diffuse or focal subarachnoid blood but without intraventricular blood; Grade II: Thin diffuse or local subarachnoid blood with intraventricular blood; Grade III: Thick focal or diffuse subarachnoid blood but without intraventricular blood; and Grade IV: Thick focal or diffuse subarachnoid blood with intraventricular blood.

Measurement of cerebral blood flow

Transcranial Doppler ultrasonography (TDU) (Multi-Dop X2, DWL, Germany) was used. Patients were placed in the supine position. A 2.0 MHz probe was used to measure the velocity of MCA at the temporal window (the zygomatic arch from the orbit to the outer edge of the auricular front). The velocity of the distal extracranial internal carotid artery (eICA) was measured just below the mandibular angle as well. All measurements were made by the same doctor. An examination was performed 1 day prior to surgery and at 1, 3, 5, 7, and 14 days after the surgery.

Clinical presentations of cerebrovascular spasm

1. Symptoms fluctuated or were progressively aggravated. 2. Changes in consciousness: Patients became drowsy or comatose or went from being comatose to being alert and then became comatose again. 3. Focal neurological signs were evaluated. 4. Patients were monitored for symptoms of increased intracranial pressure. 5. No obvious seizure, hypoxia, or electrolyte imbalance were observed apart from the possibilities of cerebral edema, delayed hemorrhage, infections or hydrocephalus after surgery. These developments also included the first four symptoms but not the CVS. A diagnosis was made if patients presented with one of the first four symptoms and signs plus the last sign[2]. Occurrence of CVS was confirmed if MCA velocity was more than 120 cm/seconds, and the Lindegaard index (a ratio of the MCA velocity to the ipsilateral eICA velocity) as detected by TDU was more than 3.

Prognosis

Follow-up was performed using the Glasgow Outcome Scale (GOS) three months after discharge[16]. Grade I: Dead; Grade II: Persistent vegetative state; Grade III: Severe disability; Grade IV: Moderate disability; and Grade V: Good recovery.

Statistical analyses

Statistical analyses were performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA). Count data were analyzed by a χ^2 test. The Student's *t* test was used for comparison of measurement data that were normally distributed and had homogeneity of variance. A rank-sum test was applied for the analysis of measurement data that were not normally distributed and lacked homogeneity of variance. $P < 0.05$ was considered statistically significant.

Results

General information

Clinical presentations after surgery: One patient had altered consciousness, two had impairment of the visual field, and two had psychiatric symptoms, two patients in the control group, three patients in the treatment group. After surgery, no reopening of the craniotomy site occurred, and no death or complications such as intracranial or wound infection, intracranial fluid, cerebrospinal fluid leakage occurred after surgery.

CVS occurred in 32 patients in the two groups. For the 32 patients, TDU examination revealed that the average MCA velocity of the nimodipine group was 154.2 cm/seconds, and the average MCA velocity of the normal saline group was 182.6 cm/seconds. The velocity in 19 of 32 patients was more than 200 cm/s, the average MCA velocity of the nimodipine group among the 19 patients was 207.1 cm/seconds, and the average MCA velocity of the normal saline group was 223.3 cm/seconds. Cerebral infarction was observed by CT/MRI in 10 patients at 48 h after the occurrence of CVS, worsened headache was found in 23 patients, reduced consciousness or coma was identified in 17 patients, motor dysfunction of the limbs became aggravated in 13 patients, and newly found motor dysfunction of the limbs was seen in 7 patients.

On the day after surgery, intracranial CT examination revealed no hematoma, ischemia, and contusion or lacerated lesions in the brains.

No significant difference in the modified Fisher scale scores was found when 5 individual grades were compared separately between the nimodipine group and the normal saline group ($P > 0.05$, Table 1).

In the nimodipine treatment group, CVS was found in 13 (25%) patients, and none occurred during the first three days after the operation. Nine patients had CVS between 4 and 7 days, and 4 had CVS between 8 and 14 days. TDU examination of the nimodipine group prior to surgery indicated that the MCA velocity was no more than 120 cm/seconds (Fig. 2A). MCA velocity was slightly higher in the nimodipine group

after surgery than that prior to surgery; however, it was no more than 120 cm/seconds (Fig. 2B). In contrast, in the normal saline group, 19 (45%) patients had CVS, 3 presented with CVS within 3 days, 11 within 4-7 days and 5 between 8 and 14 days. In meningioma patients, CVS was found in 9 (25%, 9/36) patients in the nimodipine treatment group and 14 (48.28%, 14/29) patients in the normal saline group. In glioma patients, CVS was found in 2 (20%, 2/10) patients in the nimodipine treatment group and 4 (50%, 4/8) patients in the normal saline group. In metastases patients, CVS was found in 2 (33.33%, 2/6) patients in the nimodipine treatment group and 1 (25%, 1/4) patients in the normal saline group (Figure 4). Compare CVS of different tumors patients between the two groups the occurrence of CVS was no significant difference. TDU examination of the normal saline group prior to surgery indicated that the MCA velocity was no more than 120 cm/seconds (Fig. 3A). TDU examination of the normal saline group after surgery revealed that the MCA velocity was more than 120 cm/seconds (Fig. 3B). A significant difference in the occurrence of CVS was observed between the two groups ($P < 0.05$; Table 2).

Comparison of the MCA velocity prior to surgery and after surgery in the nimodipine group and the normal saline group

There was a significant change between preoperative and postoperative the MCA velocity in the normal saline group ($P < 0.05$, Table 3); however, no significant changes were observed between preoperative and postoperative the MCA velocity in the nimodipine group.

Comparison of prognoses between the nimodipine group and the normal saline group

Grade V indicated a good prognosis, and grades I, II and III were defined as a poor prognosis. The prognosis of IV is better than that of III, but it is worse than that of V. Seventy patients had a good prognosis, 24 patients had a poor prognosis (one of these patients with a poor prognosis died). A follow-up was performed three months after surgery and showed that in the nimodipine group, 3 patients were grade II, 6 were grade III, 16 were grade IV, and 27 were grade V. In the normal saline group, 1 patient was grade I, 2 patients were grade II, 12 patients were grade III, 17 patients were grade IV and 10 patients were grade V. (Table 4). In the nimodipine group, 43 patients had a good prognosis, and 9 had a poor prognosis. In the normal saline group, 27 had a good prognosis and 15 had a poor prognosis ($P < 0.05$; Table 4). The postoperative complication could be prevented by the administration of nimodipine.

Discussion

In the present study, we showed that administration of nimodipine during and after surgery can effectively prevent the occurrence of delayed CVS and improves the prognosis of CVS. After resecting the tumor, diluted nimodipine (stock solution: normal saline=1:5) was soaked into the surgical field for 10 minutes, and then nimodipine was continuously infused via a micropump. For patients weighing less than 70 kg or having unstable blood pressure, the starting dose was 0.5 mg/h, and if the patient tolerated this dose well, the dose was increased to 1 mg/h after 2h. For patients weighing more than 70 kg, the starting dose was 1 mg/h, and if the patients tolerated this dose well, the dose was increased to 2 mg/h after 2h and administered for 14 days. Thereafter, nimodipine was administered orally (60 mg, once a

day, for 7 days). CVS after intracranial tumor craniotomy is a multifactorial clinical syndrome. CVS is caused by an extreme contraction of the arteries and tense vascular smooth muscle[14]. The mechanisms underlying CVS remain unclear; it may be multifactorial and involve a complicated pathological process. Potential causes of CVS are as follows: 1. mechanical stimulation such as damage, compression or stretching of the blood vessels during surgery, leading to the blood flowing into the subarachnoid space and subsequent occurrence of CVS occurs[17]; 2. vascular wall injury caused by compression of the vascular wall and vascular wall malnutrition[18]; 3. damage caused by the oxidation of hemoglobin to methemoglobin and release of oxygen free radicals[19]; 4. constriction of the blood vessels caused by vasoactive substances[20]; 5. increased intracranial pressure, the overdose of dehydration drugs and insufficient supply of blood volume[21]; and 6. inflammation and immune reactions of blood vessel walls[6, 22, 23]. The common final pathway arising from all the above factors stated is a change in the permeability of smooth muscle cells in the blood vessels, an increase in calcium influx and release of calcium ion from intracellular calcium stores, leading to an overload of free calcium in the cytosol[24]. When a critical constriction concentration is reached following the opening of calcium channels, extracellular calcium enters the cells and is released from the calcium stores, leading to an increase in the concentration of free calcium in the cytosol; thus, vasospasm occurs[25]. Therefore, calcium overload is believed to be the most important phenomenon during the generation of vasospasm.

There are two types of calcium channels, voltage-dependent and receptor-operated[26]. The former is located in the cell membrane of heterologous multimeric transmembrane proteins. These channels are activated at depolarized membrane potentials and are the source of the "voltage-dependent" epithet. The concentration of calcium (Ca^{2+} ions) is normally several thousand times higher outside of the cell than inside. Activation of particular VDCCs allows Ca^{2+} to rush into the cell, which depending on the cell type, results in activation of calcium-sensitive potassium channels, muscular contraction, excitation of neurons, upregulation of gene expression, or release of hormones or neurotransmitters. The opening of this type of channel is related to voltage and occurs due to the depolarization of the smooth muscle cell membrane after the channel is activated and excited[27]. The opening of the latter channel is caused by the stimulation of receptors of the cell membrane by certain substances, such as 5-hydroxytryptamine and adrenalin. Subsequently, calcium influx increases, and calcium release occurs, leading to vasospasm caused by the abovementioned mechanism. These findings provide evidence for the potential prevention of CVS using calcium channel blockers.

It has been shown that nimodipine significantly reduced symptoms caused by secondary ischemia after SAH; consequently, the risks of death and paralysis caused by CVS were markedly reduced[28]. Currently, nimodipine is considered as the first choice for the prevention of CVS after SAH. Nimodipine is a second-generation dihydrotestosterone pyridine class calcium antagonist with the highest lipid solubility[29]. High lipophilicity of nimodipine facilitates its movement through the blood-brain-barrier, and nimodipine is also highly selective for vascular smooth muscle due to the dihydrotestosterone pyridine ring[30]. Moreover, nimodipine can block L-type voltage-dependent calcium channels in the cell membrane of vascular smooth muscles, effectively inhibiting calcium influx and simultaneously activating Ca^{2+} -ATP,

which promotes depletion of cytoplasmic calcium and enhances calcium intake and storage from the mitochondria and endoplasmic reticulum, thereby regulating the concentration of intracellular Ca^{2+} and maintaining normal physiological functions[31]. Moreover, nimodipine can inhibit aggregation of platelets and leukocytes, reducing erythrocyte rigidity and blood viscosity and preventing the release of 5-HT and arachidonic acid and other vasoactive substances that cause vasoconstriction[32].

In addition, nimodipine can significantly improve cerebral blood circulation after brain injury, preventing secondary brain damage and promoting brain function recovery. Nimodipine lavage can effectively improve the prognosis of secondary cerebral vasospasm after SAH[33-35]. Our findings revealed that infusion and oral intake of nimodipine after nimodipine lavage during surgery are effective in the prevention of the development of delayed CVS after intracranial tumor craniotomy. The incidence of CVS in the nimodipine group (25%) was significantly lower than that in the normal saline group (45%). In addition, the MCA velocity was significantly lower in the nimodipine group than in the normal saline group after surgery. Prognoses appeared to be remarkably improved in the nimodipine group.

To date, regarding the diagnosis of CVS after intracranial tumor craniotomy, digital subtraction angiography (DSA) and TDU are believed to be effective CVS detection methods. DSA had been a gold standard for the diagnosis of CVS[36]. However, if the blood vessel is too small to be detected by DSA, misdiagnosis of CVS might occur[37]. Because DSA is an invasive examination and could produce risks such as iatrogenic stroke and rupture of the blood vessels, the application of DSA is limited for the detection of CVS[26, 38]. Additionally, TDU has the advantage of being economical, non-invasive, real-time, and repeatable, offering continuous monitoring with high sensitivity and specificity; thus, TDU has become the first-line procedure in the detection of CVS[39]. Blood flow velocity (V_{BF}) is determined by cerebral blood flow (Q) and the diameter of cerebral blood vessels (D). The formula is as follows: $V_{BF} = 4Q/D^2$, with the velocity being inversely proportional to the diameter when blood volume does not change[40]. Smaller blood vessels have faster blood flow velocity; therefore, hemodynamic changes, such as high velocity and high resistance, can occur. Thus, the extent of blood vessel narrowing can be estimated by the alteration of blood flow velocity. Moreover, the MCA is the best blood vessel for monitoring CVS[41, 42]. The human MCA is a terminal branch of the ICA, has few collateral branches and has a long and straight stem. The MCA is easily detected, has high specificity, and its diameter is negatively correlated with the blood flow velocity and is positively correlated with vasospasms. Based on these facts, the MCA is typically examined to detect CVS.

In this study, blood flow velocity prior to CVS was measured as baseline velocity and was compared with that after surgery at different time points. Furthermore, comparing changes in blood flow velocity in the MCA allows the objective detection of CVS. However, different operators of TDU might obtain different results due to unavoidable subjective factors such as the variable angle of the ultrasound probe that was used[43]. In this study, the same doctor performed TDU examinations in all patients, which made the examination data reliable. Our results showed that TDU can be effectively used for the diagnosis of CVS after intracranial tumor surgery. If the flow velocity in the MCA is more than 120 cm/s, and Lindegaard index is more than 3, a diagnosis of CVS is confirmed.

We showed that the application of nimodipine during and after surgery can effectively prevent the occurrence of delayed CVS and improve the prognosis of CVS. Notably, the retrospective cases in our study were limited. If larger sample sizes are available, general problems can be studied more clearly.

Conclusions

Nimodipine can significantly reduce ischemia secondary to CVS after intracranial surgery; consequently, it markedly reduces the risks of mortality and morbidity and improves prognoses.

Declarations

Ethics approval and consent to participate: This trial was approved by the local ethics committee at First hospital of Jilin University (2011-041). Informed written consent was taken from all participants.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

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Authors' Contributions: FC is the guarantor of integrity of the entire study. YY and LYQ gave the study concepts and designed the study. YY, YQL, ZJ, SZ and FC did the literature research. YY performed the data analysis. YY performed the statistical analysis. YY and FC prepared the manuscript draft and FC did edit the final manuscript. All co-authors approved the final submitted manuscript.

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List Of Abbreviations

CVS: cerebral vasospasm

MCA: middle cerebral artery

elCA: extracranial internal carotid artery

GOS: Glasgow Outcome Scale

SAH: subarachnoid haemorrhage

CT: computed tomography

TDU: Transcranial Doppler ultrasonography

VDCCs: Voltage-dependent calcium channels

DSA: digital subtraction angiography

V_{BF} : Blood flow Velocity

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Tables

Table 1. Modified Fisher Scale (brain on the day of surgery)

Groups	Modified Fisher Scale (grade)				Total
	I	II	III	IV	
Treatment	29	12	10	1	52
Control	28	9	4	1	42
Total	57	21	14	2	94

$P=0.5774$

Table 2. Comparison of CVS between the two groups

Groups	CVS	No CVS	Total
Treatment	13	39	52
Control	19	23	42
Total	32	62	94

$P=0.0395$

Table 3. Comparison of MCA velocity between groups (cm/s) (mean±SD)

Groups	Cases	Prior to treatment	1 day	3 days	5 days	7 days	14 days
Treatment	52	98.8±34.9	101.6±32.2	99.3±32.0	99.4±32.9	103.5±38.5	104.8±35.9
Control	42	96.9±29.6	121.4±33.7*	129.0±43.4*	135.6±46.1*	154.5±42.3*	136.9±49.6*

*compared with prior to the treatment $P < 0.05$.

Table 4. Comparison of GOS between the two groups.

Groups	GOS scale (grade)					Total
	I	II	III	IV	V	
Treatment	0	3	6	16	27	52
Control	1	2	12	17	10	42
Total	1	5	18	33	37	94

$P=0.0389$

Figures

Figure 1

A: The exposure of the optic nerve and the MCA in the sellar region operation. LICA is the left ICA. LMCA is the left MCA. B: Nimodipine lavage of the optic nerve and MCA in the sellar region operation. LICA is left ICA.

Figure 2

A: TDU examination of the treatment group prior to surgery. The MCA velocity was 106 cm/second. B: TDU examination of the treatment group after surgery. The MCA velocity was 113 cm/second.

Figure 3

A: TDU examination of the control group prior to surgery. The MCA velocity was 85 cm/second. B: TDU examination of the control group after surgery. The MCA velocity was 273 cm/second.

Figure 4

A. Compare CVS of meningioma patients between the nimodipine treatment group and the normal saline group, the occurrence of CVS was no significant difference. $p=0.0511$. B. Compare CVS of glioma patients between two groups, the occurrence of CVS was no significant difference. $p=0.1797$. C. Compare CVS of metastases patients between two groups, the occurrence of CVS was no significant difference. $p=0.7782$.