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Research Article
Evaluating the Efficacy of Carmustine Combined with Temozolomide in the Treatment of Glioma Following Minimally Invasive Surgery

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Abstract

Background and Objective: Temozolomide is more beneficial than Carmustine in reducing tumor size, prolonging survival time and improving quality of life in patients with gliomas. However, there are fewer domestic and international reports on the feasibility and safety of the combined use of the two. This study observed the efficacy of Carmustine combined with Temozolomide in the treatment of glioma following minimally invasive surgery. **Materials and Methods:** A retrospective analysis of clinical data from 81 glioma patients who underwent microscopic glioma resection at Affiliated Hospital of Hebei University of Engineering between February, 2019 and February, 2021 was conducted. Patients were divided into a control group (n = 41, post-surgical resection with tumor cavity placement of Carmustine slow-release implant) and an experimental group (n = 40, oral Temozolomide in addition to the control group). The efficacy, serum levels of angiogenesis-related factors, neuropeptide levels, inflammatory and chemokine levels, daily living ability, neurological function, survival rate and adverse effects were compared between the two groups. **Results:** Serum levels of neurotensin (NT), somatostatin (SS), Monocyte Chemotactic Protein-1 (MCP-1) and the Glasgow Coma Scale (GCS) scores were significantly higher in the experimental group than in the control group ($p<0.05$). There was no statistically significant difference in the incidence of gastrointestinal symptoms, hematologic toxicity and hepatorenal toxicity between the two groups ($p>0.05$). **Conclusion:** Carmustine combined with Temozolomide showed a definite efficacy in patients with glioma after microscopic glioma resection.

Key words: Glioma, microscopic glioma resection, Carmustine, Temozolomide, angiogenesis, neuropeptide, inflammatory response

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INTRODUCTION

Glioma is a prevalent primary intracranial neoplasm of the central nervous system, with astrocytoma and glioblastoma multiforme being the most common subtypes[1]. According to the Central Brain Tumor Registry of the United States (CBTRUS)[2], gliomas account for approximately 80% of cranial malignancies and 27% of central nervous system tumors. Gliomas exhibit three principal characteristics: Uncontrolled cell proliferation, indistinct tumor boundaries and high aggressiveness. These tumors infiltrate the brain, displaying unrestricted cell differentiation and growth, frequently causing erosion and damage to surrounding normal tissues and organs[3,4]. Infiltration of surrounding brain tissues often complicates complete surgical resection and results in postoperative residual tumor cells. Consequently, adjuvant treatment modalities are typically required after surgery to further eliminate tumor cells and reduce the risk of recurrence.

Local chemotherapy involves the implantation of drugs into the surgical residual cavity, enabling the maintenance of high local drug concentrations within the tumor, which aids in reducing local recurrence rates and improving survival outcomes. Carmustine, also known as carazolam, is a classic chemotherapeutic agent that alkylates the oxygen atom at the sixth position of guanine in DNA, causing DNA strand cross-linking, disrupting DNA structure and function and impeding normal DNA replication processes, ultimately inhibiting cancer cell replication[5,6]. Early clinical trials have demonstrated that Gliadel, a local extended-release chemotherapy formulation containing Carmustine, improved median survival in patients with recurrent glioma from 5.4 to 7.2 months[7]. However, Carmustine is frequently combined with other chemotherapeutic agents due to its associated adverse effects, including gastrointestinal symptoms, bone marrow suppression and hepatorenal toxicity.

Temozolomide, a second-generation novel alkylating agent, penetrates the blood-brain barrier, entering the cerebrospinal fluid and exerts anti-tumor invasion, metastasis and anti-angiogenic effects by interfering with DNA repair in malignant tumor cells and inhibiting endothelial cell repair[8]. Studies have confirmed that, compared to Carmustine, Temozolomide is more advantageous in reducing tumor volume, extending survival duration and enhancing the quality of life in patients with malignant gliomas[9]. However, there is limited literature on the feasibility and safety of combining these two agents. Thus, this study conducted a retrospective analysis of the clinical data of 81 glioma patients who underwent microscopic glioma resection, examining the effects of Carmustine combined with Temozolomide on angiogenesis, neuropeptide levels, inflammatory response and survival rates following minimally invasive surgery.

MATERIALS AND METHODS

Clinical data: The clinical data of 81 patients with glioma who underwent microscopic glioma resection at Affiliated Hospital of Hebei University of Engineering from February, 2019 to February, 2021 were retrospectively analyzed and stratified into two groups based on their postoperative treatment regimens. The control group comprised 41 cases, including 22 males and 19 females, aged 32-74 years, with a mean age of (44.25±4.84) years, body mass index (22.36±2.15) kg m^{-2}, glioma classification based on the KPS scale: 20 cases of grade III and 21 cases of grade IV, tumor location: 19 cases of infratentorial cerebellar and 22 cases of supratentorial cerebellar. The experimental group consisted of 40 cases, including 21 males and 19 females, aged 30-76 years, with a mean age of (45.84±4.38) years, body mass index (22.54±2.27) kg m^{-2}, KPS scale glioma grade: 22 cases of grade III and 18 cases of grade IV, tumor location: 17 cases of infratentorial and 23 cases of supratentorial. The baseline data of the two groups were well-balanced ($p>0.05$) and comparable.

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the diagnostic criteria for glioma[10], postoperative pathology confirmed as grade III or IV astrocytoma or glioblastoma multiforme, no radiotherapy or chemotherapy before surgery, Karnofsky Performance Status (KPS) score>60, expected survival time>3 months, complete clinical data. This study was approved by the Ethics Committee of the Affiliated Hospital of Hebei University of Engineering. The research objects were informed and they signed a fully-informed consent form.

Exclusion criteria: Patients with concomitant other malignant tumors, severe impairment of other vital organ functions, such as heart, liver, kidney and bone marrow, coexisting immune system, hematological system and endocrine system diseases, glioma recurrence, grade II cardiac insufficiency, arrhythmia, myocardial infarction and myocardial ischemia, allergy to drugs used in this study, tumor located in the ventricle and intraoperative ventricular rupture diameter >5 mm, history of radiotherapy for brain lesion implantation or local implantation chemotherapy, pregnancy or lactation and loss to follow-up.

Methods: Carmustine (SFDA drug clinical trial lot number 2008L03423) used in this study was based on ethylene glycolate mono propylene glycolate copolymer (PLGA) as the carrier (developed and produced by Shandong Lanjin Company), with a round shape, each tablet containing 20 mg of Carmustine, with a thickness of 1 mm and a diameter of 14 mm and stored at a temperature between 2-10°C. All patients underwent microscopic glioma resection. Following tumor removal and complete hemostasis, 3-12°C Carmustine slow-release implants were placed according to the size of the tumor cavity. In cases with ventricular rupture diameter $\leq$5 mm, the Carmustine slow-release implant was inserted into the tumor cavity aided by a gelatin sponge seal and the meningeal defect was repaired with sutures or non-absorbable artificial repair material, without placing a drain. The scalp was sutured and bandaged with pressure. The experimental group received postoperative oral Temozolomide in addition to the control group's treatment, i.e., Temozolomide capsules (State Drug Administration H20223523, 100 mg, Suzhou Terry Pharmaceutical Co. Ltd.) were administered orally on an empty stomach for 5 days, with 28 days constituting one treatment course. Patients underwent 2-6 treatment courses based on their tolerance, with a minimum of 2 courses. The initial course dose was 150 mg/m^2/day, if the patient's platelet count was $\geq 100\times10^9$/L and neutrophils were $\geq 1.5\times10^9$/L, the subsequent course dose increased to 200 mg/m^2/day, if the patient's neutrophil count was $<1.5\times10^9$/L within one course, the following course dose decreased by 50 mg/m^2/day, but not lower than the minimum recommended dose of 100 mg/m^2/day.

Observation indices

Treatment efficacy: After 2 treatment courses, patients' efficacy was assessed according to RECIST 1.1 criteria[11]: Complete disappearance of all measurable lesions with a maintenance period >4 weeks was considered complete remission (CR), at least a 50% reduction in the product of the sum of the largest diameter and the transverse diameter of each lesion with a maintenance period >4 weeks was considered partial remission (PR), the sum of the product of the largest diameter of each lesion with a reduction of not more than 50% or an increase of not more than 25% was considered stable disease (SD), the disease was considered progressive (PD) if the total product of the maximum diameter of the lesions increased by more than 25% and new lesions appeared:

$$\text{Overall response rate (ORR)} = \text{CR+PR}$$

Laboratory indices: Fasting venous blood (3 mL) was collected from patients before and after 2 treatment courses and the serum was separated (rested for 30 min at room temperature and centrifuged at 3,000 rpm with a radius of 6 cm for 10 min). Hepatocyte Growth Factor (HGF), Tumor Necrosis Factor-α (TNF-α), Interleukin-17 (IL-17), Monocyte Chemotactic Protein-1 (MCP-1) levels and β-endorphin (β-EP), arginine vasopressin (AVP), neurotensin (NT) and somatostatin (SS) levels were assessed.

Activities of daily living and neurological functions: Activities of daily living (ADL) assessment included 10 items such as bathing, grooming and toileting, with a total of 100 points and the ability to perform daily activities was directly proportional to the score. The Glasgow Coma Scale (GCS) evaluated eye response, speech and limb movement, with a score range of 0-15, a higher score indicated better neurological status. These assessments were conducted before treatment and after 2 treatment courses.

Survival: Telephone follow-up, condition record form, or outpatient follow-up was performed every 3 months since the patient's first treatment administration and the follow-up continued for 2 years, with the final follow-up deadline in February, 2023. Survival rates at 6, 12 and 24 months of follow-up were calculated for both groups.

Adverse reactions: Adverse drug reactions, including gastrointestinal reactions, hematologic toxicity and hepatorenal toxicity, were analyzed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)[12].

Statistical analysis: Data were processed using SPSS 23.0 software and measurement data conforming to normal distribution were expressed by Mean±Standard Deviation (mean±SD). The between-group comparisons were analyzed by means of independent sample t-tests and the within-group comparisons were analyzed by means of paired sample t-tests. Categorical data were expressed as several cases or percentages (n%) and compared using the Chi-square Test. Kaplan-Meier survival curves were constructed and analyzed using the Log-rank χ^2 test. A $p<0.05$ was considered to indicate a statistically significant difference.

RESULTS

Clinical efficacy: The overall response rate (ORR) of the experimental group (65.00%) was significantly higher ($p<0.05$) than that of the control group (34.15%) Table 1.

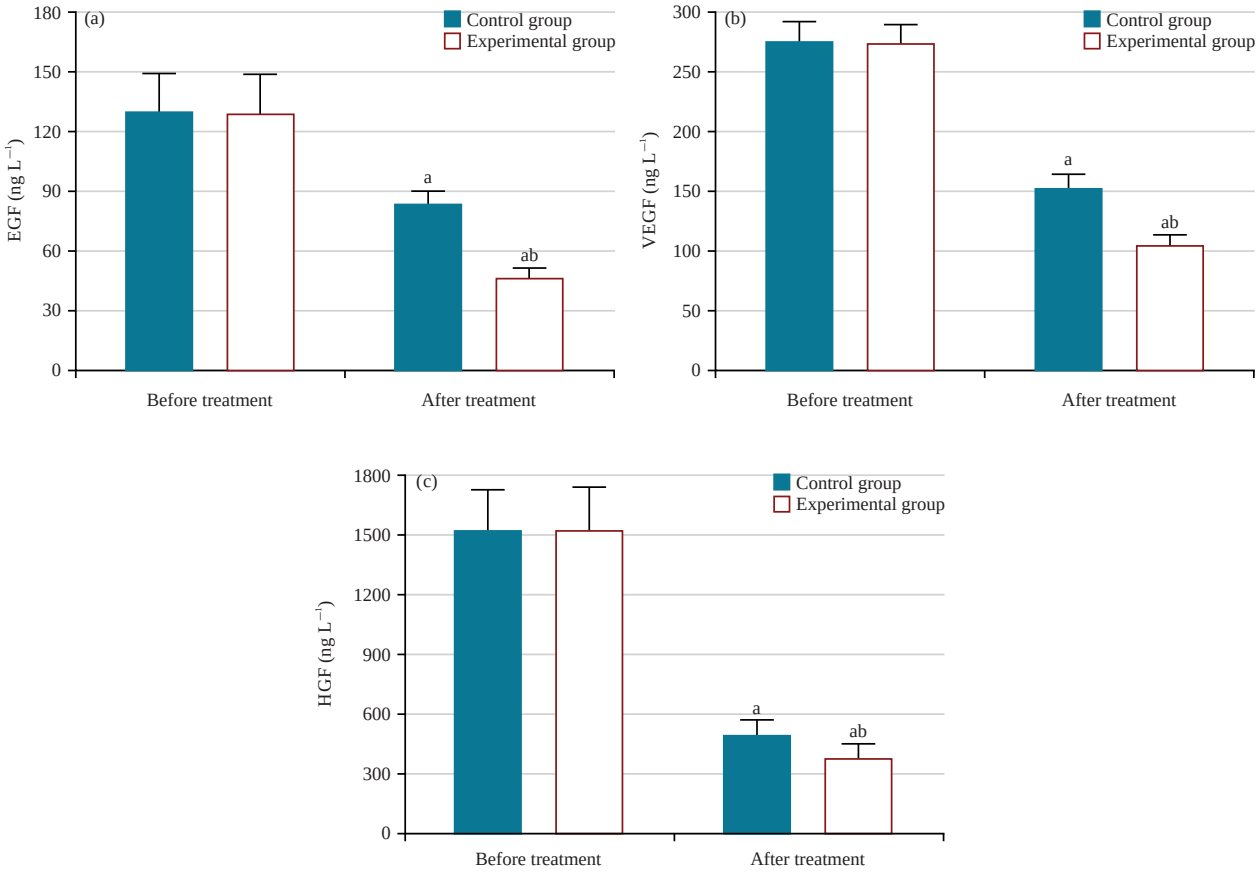

Fig. 1(a-c): Effect of Carmustine combined with Temozolomide treatment on serum angiogenesis-related factor levels in glioma patients after minimally invasive surgery, (a) EGF, (b) VEGF and (c) HGF levels in glioma patients

Carmustine combined with Temozolomide treatment after minimally invasive surgery significantly reduced serum, compared to the same group before treatment, [a]p<0.001, compared to the control group, [b]p<0.001, EGF: Epidermal growth factor, VEGF: Vascular endothelial growth factor and HGF: Hepatocyte growth factor

Table 1: Comparison of efficacy n (%)

Group	Number of cases	CR	PR	SD	PD	ORR
Control group	41	0 (0.00)	14 (34.15)	20 (48.78)	7 (17.07)	14 (34.15)
Study group	40	1 (2.50)	25 (62.50)	9 (22.50)	5 (12.50)	26 (65.00)
$\chi 2$						7.711
p						0.006

CR: Complete remission, PR: Partial remission, SD: Stable disease, PD: Progressive disease and ORR: Overall response rate

Serum angiogenesis-related factor levels: No significant differences were observed in serum EGF, VEGF and HGF levels before treatment between the experimental and control groups (p>0.05). Serum EGF, VEGF and HGF levels decreased in both groups after treatment compared to before treatment (p<0.05) and these levels were lower in the experimental group after treatment compared to the control group (p<0.05) Fig. 1(a-c).

Neuropeptide levels: No significant differences were observed in serum β-EP, AVP, NT and SS levels before treatment between the experimental and control groups (p>0.05). After treatment, serum β-EP and AVP levels decreased, while NT and SS levels increased in both groups compared to before treatment (p<0.05). Furthermore, serum β-EP and AVP levels were lower and NT and SS levels were higher in the experimental group compared to the control group after treatment (p<0.05) Fig. 2(a-d).

Inflammatory factors and chemokines: No significant differences were observed in serum TNF-α, IL-17 and MCP-1 levels before treatment between the experimental and control

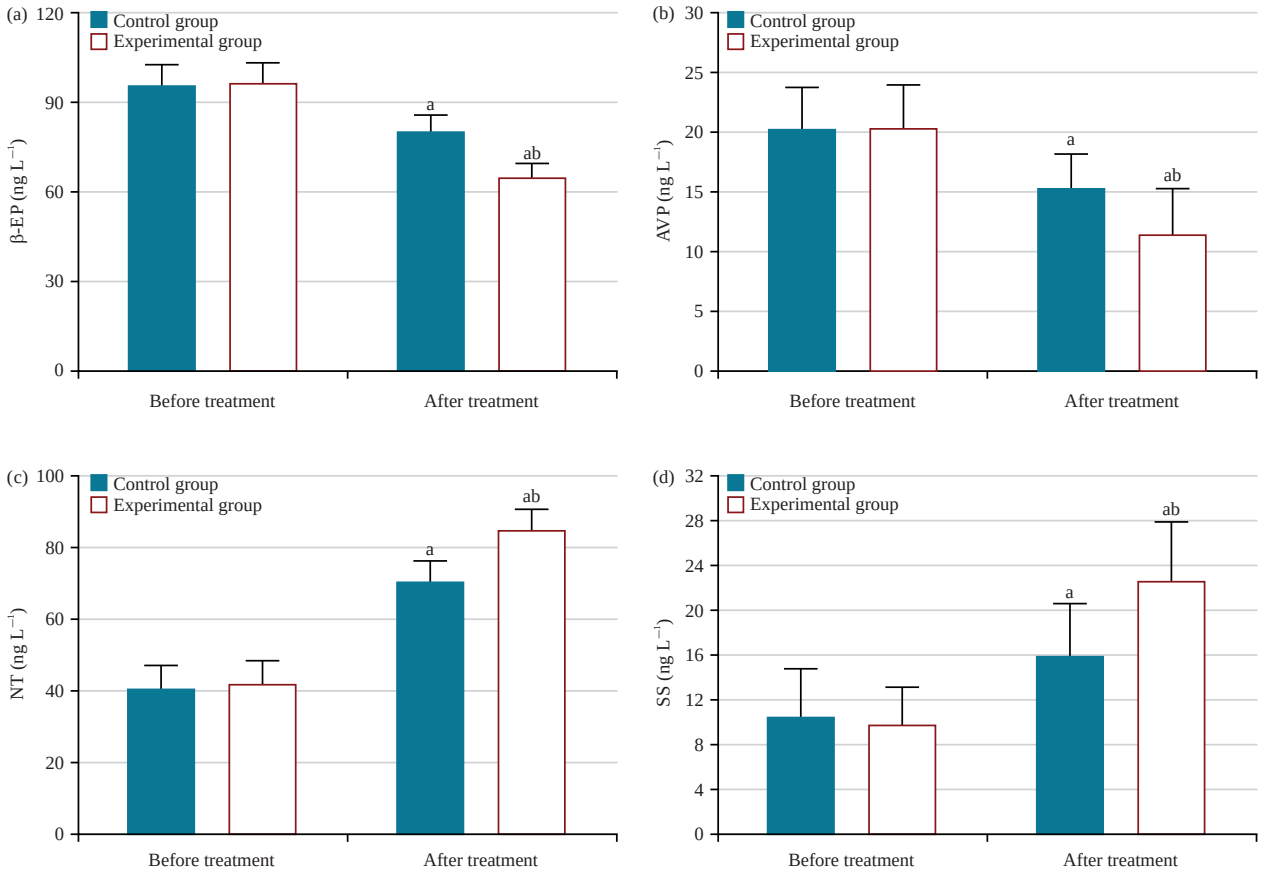

Fig. 2(a-d): Effect of Carmustine combined with Temozolomide treatment on serum neuropeptide levels in patients with glioma after minimally invasive surgery, (a) β-EP, (b) AVP levels and increased, (c) NT and (d) SS levels in glioma patients

Carmustine combined with Temozolomide treatment after minimally invasive surgery significantly reduced serum, compared to the same group before treatment, [a]p<0.001, compared to the control group, [b]p<0.001, β -EP: β-endorphin, AVP: Arginine vasopressin, NT: Neurotensin and SS: Somatostatin

Table 2: Comparison of 2-year survival rates n (%)

Group	Number of cases	6 months	12 months	24 months
Control group	41	30 (73.17)	21 (51.22)	17 (41.46)
Experimental group	40	34 (85.00)	26 (65.00)	22 (55.00)
$\chi 2$		1.250	1.290	1.251
p		0.264	0.256	0.263

groups (p>0.05). Serum TNF-α and IL-17 levels decreased, while MCP-1 levels increased in both groups after treatment compared to before treatment (p<0.05). Serum TNF-α and IL-17 levels were lower and MCP-1 levels were higher in the experimental group compared to the control group after treatment (p<0.05) Fig. 3(a-c).

Activities of daily living and neurological functions: No significant differences were observed in ADL, NIHSS and GCS scores before treatment between the experimental and control groups (p>0.05). After treatment, ADL and NIHSS scores decreased and GCS scores increased in both groups compared to before treatment (p<0.05). In the experimental group, ADL and NIHSS scores were lower and GCS scores were higher compared to the control group after treatment (p<0.05) Fig. 4(a-c).

Survival rate: There were no statistically significant differences in survival rates at 6, 12 and 24 months between the experimental and control groups (p>0.05), as shown in Table 2. Kaplan-Meier survival curves were constructed, with a median survival time of 15 months (95% CI: 12.315-17.685) in the control group and 17.6 months (95% CI: 15.100-20.100) in the experimental group. The difference was not statistically significant according to the Log rank χ^2 test ($\chi^2 = 1.782$, $p = 0.182$) Fig. 5.

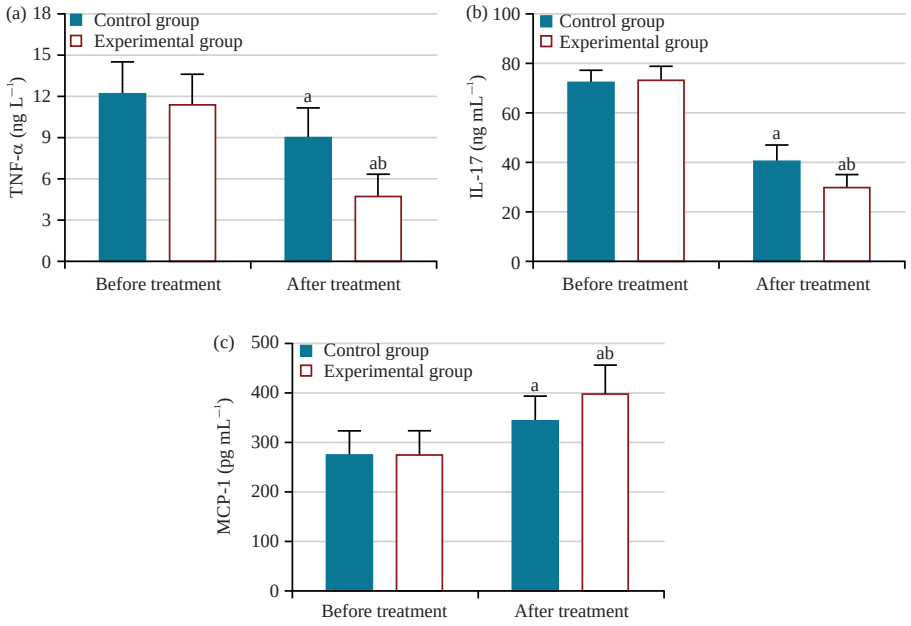

Fig. 3(a-c): Effect of Carmustine combined with Temozolomide treatment on serum inflammatory and chemokine levels in patients with glioma after minimally invasive surgery, (a) TNF-α, (b) IL-17 levels and increased and (c) MCP-1 levels in glioma patients

Carmustine combined with Temozolomide treatment after minimally invasive surgery significantly reduced serum, compared to the same group before treatment, [a]p<0.001, compared to the control group, [b]p<0.001, TNF-α: Tumor Necrosis Factor-α, IL-17: Interleukin-17 and MCP-1: Monocyte Chemotactic Protein-1

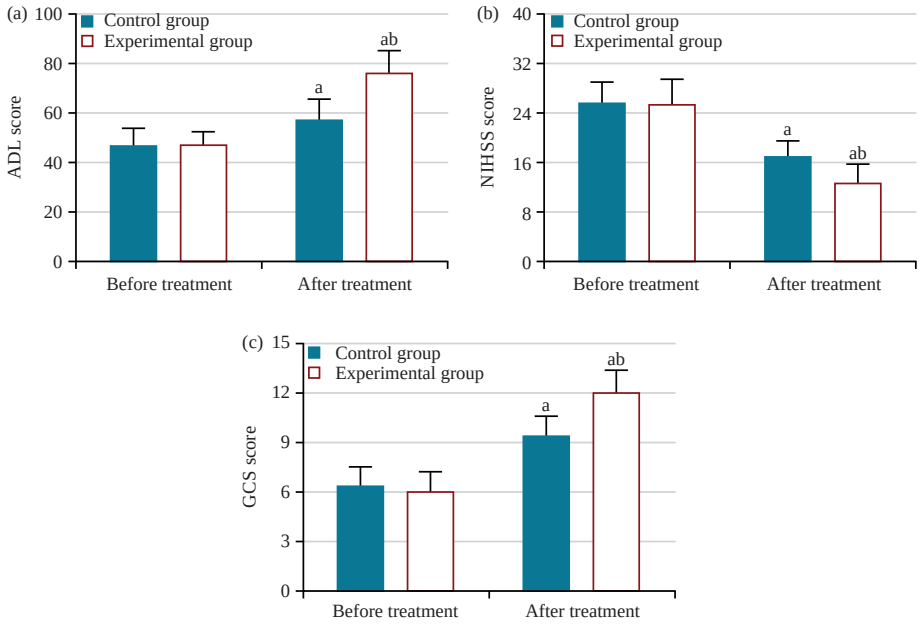

Fig. 4(a-c): Effect of Carmustine combined with Temozolomide treatment after minimally invasive surgery on daily living ability and neurological function level of glioma patients, (a) ADL, (b) NIHSS levels and decreased and (c) GCS levels in glioma patients

Carmustine combined with Temozolomide treatment after minimally invasive surgery significantly increased, compared to the same group before treatment, [a]p<0.001, compared to the control group, [b]p<0.001, ADL: Activities of daily living, NIHSS: National Institutes of Health Stroke Scale and GCS: Glasgow coma scale

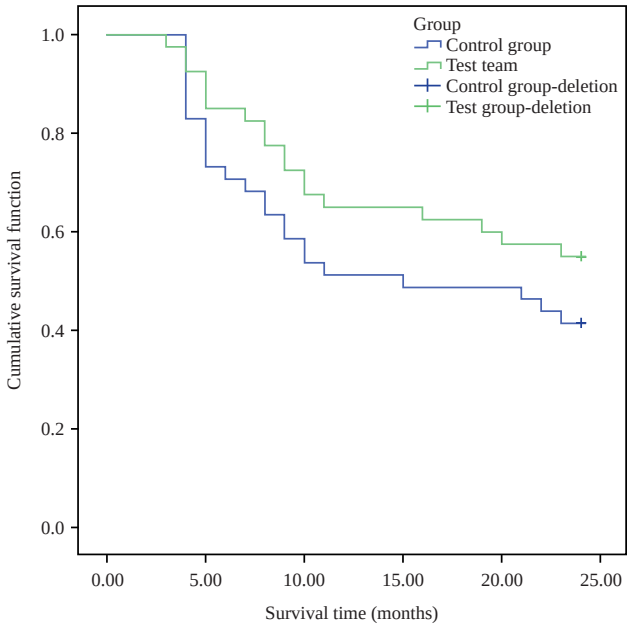

Fig. 5: Survival function plot for both groups

Table 3: Comparison of adverse reactions n (%)

Group	Number of cases	Gastrointestinal symptoms	Hematologic toxicity	Hepatic and renal toxicities
Control group	41	12 (29.27)	8 (19.51)	6 (14.63)
Experimental group	40	14 (35.00)	9 (22.50)	7 (17.50)
χ^2		0.228	0.075	0.092
p		0.633	0.785	0.762

Adverse reactions: Adverse reactions in both groups primarily included gastrointestinal reactions (nausea and vomiting), hematotoxicity and hepatorenal toxicity, with no other adverse reactions observed. There were no statistically significant differences in the incidence of gastrointestinal reactions, hematologic toxicity and hepatorenal toxicity between the two groups (p>0.05) Table 3.

DISCUSSION

Microscopic glioma resection is a prevalent procedure for glioma treatment. By accurately locating the tumor and delineating the boundary between the tumor and brain tissue using a microscope, the tumor lesion can be maximally removed, thereby prolonging patient survival after surgery. However, minimally invasive surgery has inherent limitations. Although most imaging procedures entail "total resection", the tumor is excised along the brain gyrus and sulcus boundaries and anatomically resected along the white matter fiber bundle of the tumor margin. It is challenging to distinguish the edema zone, tumor margin infiltration zone and surrounding normal brain tissue under the microscope, rendering rapid and accurate boundary assessment difficult. Consequently, residual tumor cells often remain after surgery[13,14]. Therefore, postoperative chemotherapy has become crucial for glioma treatment and recurrence prevention.

Carmustine extended-release agent is an interstitial chemotherapeutic agent placed into the tumor cavity after resection, directly acting on the tumor resection site to inhibit DHA post-synthesis and enhance cytotoxic effects, thus eliminating residual tumor cells[15]. The State Food and Drug Administration (FDA) approved it for recurrent malignant glioma in 1996, followed by the addition of incipient glioma to its indications in the United States and other European countries in 2003 and 2004. In a study of human glioma BT325 cells, Guo *et al.*[16] observed that Carmustine-loaded micelles increased cytotoxicity and induced apoptosis. Barr and Grundy[17] included 59 patients with primary glioma who were implanted with Carmustine retardant during surgery and used the Kaplan-Meier method to calculate survival time, finding that the median survival time was 15.3 months, with postoperative complications in 8 (13.5%) patients. Champeaux and Weller[18] reported in a 9 year

national retrospective study that the median overall survival (OS) of 1659 patients with primary or recurrent high-grade glioma was 1.4 years (95% CI:1.3-1.5), with OS at years 1 and 2 of 66% (95% CI:63.7-68.5) and 32.3% (95% CI: 29.9-35). These domestic and international studies highlight the benefits of postoperative adjuvant Carmustine in prolonging glioma patient survival, though safety improvements are still needed. Temozolomide is a novel oral alkylating agent that acts on the DNA replication stage, inhibiting DNA replication and hindering tumor progression. Chen *et al*.[19] reported that a double-sensitive hydrogel delivery system (loaded with synergistic chemotherapeutic drugs Carmustine and Temozolomide) was injected intracavitary after glioma resection, finding that the median patient survival was 65 days-twice as long as the resection-only group-indicating that the combination of the two drugs effectively inhibits tumor recurrence and prolongs patient survival. Burri *et al*.[20] reported that a treatment regimen of intraoperative implantation of Carmustine extended-release+postoperative oral Temozolomide extended the median patient survival from 8.5 months to 18 months and improved the 1-year survival rate without significantly increasing the toxic side effects of the combined treatment. In this study, the ORR was higher in the experimental group (65.00%) than in the control group (34.15%) and serum β-EP and AVP levels, along with ADL and NIHSS scores, were lower after treatment than in the control group. Conversely, NT and SS levels, along with GCS scores, were higher than in the control group and no significant differences were observed in the incidence of adverse effects. These results indicated that glioma patients undergoing microscopic glioma resection followed by Carmustine combined with Temozolomide treatment demonstrated significant effectiveness in regulating neuropeptide levels and improving neurological function and activities of daily living. Further analysis using Kaplan-Meier survival curves revealed that the difference in overall survival rate and median survival time between the two groups was not significant, which deviates slightly from the findings of the aforementioned domestic and international studies and may be attributable to the small sample size included in this study. Thus, it remains necessary to expand the sample size and extend the follow-up time in future studies to further investigate the combination regimen's impact on glioma patient prognosis in the short and long term.

Neovascularization in tumor tissue serves as the link between the body and the tumor, supplying nutrients to the tumor and promoting metabolite elimination. The degree of neovascularization is closely related to malignant behaviors such as invasiveness and proliferation of tumor cells. In glioma, abnormal vascular endothelial cell proliferation in tumor tissue leads to neovascularization, which stimulates endothelial cell proliferation and contributes to tumor growth, survival and metastasis[21]. The VEGF is a major regulator of angiogenesis and primarily promotes tumorigenesis and progression by regulating microvascular density (MVD) and endothelial cell function, modulating pro-inflammatory responses, inhibiting mature dendritic cells and endothelial cell apoptosis and other mechanisms. It has been confirmed that VEGF-mediated invasion along the vascular basement membrane is a common invasive pathway in gliomas, indirectly verifying that VEGF can contribute to glioma cell invasion and metastasis[22]. The binding of EGF to the epidermal growth factor receptor can cause the conversion of the cell membrane or intracellular tyrosine residue-specific protein kinases from inactivated to active forms, activating many downstream cell signaling pathways, inhibiting apoptosis and promoting angiogenesis. Abnormally elevated HGF promotes extracellular matrix breakdown and increases the invasive and proliferative capacity of glioma cells. The MCP-1 can be secreted by various tissue cells and has chemotactic inflammatory cell infiltration, tumor cell growth promotion and anti-tumor immune response inhibition functions. It exerts chemotactic effects on TAMs, prompting them to secrete IL-8 and VEGF, thereby stimulating local tissue vascularization and inducing angiogenesis. In this study, serum EGF, VEGF, HGF, TNF-α and IL-17 levels were lower, while MCP-1 levels were higher in the experimental group than in the control group after treatment. This confirmed that Carmustine combined with Temozolomide can inhibit angiogenesis and hinder tumor metastasis and proliferation in glioma patients after minimally invasive surgery. The reasons for this may include: (1) Carmustine causing metabolic disorders in vascular endothelial cells, increasing vascular resistance, thickening the vessel wall and reducing blood supply to tumor cells, Carmustine blocking growth factor receptor (GDFR) signaling and reducing tumor angiogenesis and Carmustine inhibiting angiogenesis by down-regulating cytokine expression, such as VEGF and TNF-α[23], (2) Temozolomide attacks tumor cell DNA and destroys the DNA alkylation base, preventing the 6th oxygen atom on guanine from finding paired bases, which affects the normal replication of DNA and subsequently triggers autophagy or apoptosis of tumor cells, thereby inhibiting tumor cell growth and neovascularization[24,25].

This study observed the effect of postoperative treatment with Carmustine combined with Temozolomide in glioma patients, which provides new ideas and expands the treatment options for glioma patients after surgery. However, there are some shortcomings in this study. As it is the first study, the number of cases is small and it is a single-center

study, which may cause some bias in the data. In addition, the observation time was relatively short and only its effect on the short-term survival rate was observed, whether it can improve the long-term survival rate still needs to further expand the number of cases and prolong the observation time for further exploration and analysis.

CONCLUSION

Glioma patients treated with Carmustine combined with Temozolomide after microscopic glioma resection demonstrated a significant effectiveness in inhibiting angiogenesis, modulating neuropeptide levels, reducing inflammatory responses, ameliorating the extent of neurological dysfunction and enhancing the ability to perform daily activities without significantly increasing adverse effects. However, the combination therapy did not significantly impact short-term survival.

SIGNIFICANCE STATEMENT

Carmustine is a recognized classical chemotherapeutic agent for gliomas, but it is often used in combination with other chemotherapeutic agents due to the presence of adverse reactions such as gastrointestinal reactions, myelosuppression and hepatic and renal toxicity. Temozolomide belongs to the second generation of new alkylating agents, which are more conducive to reducing tumor volume, prolonging survival time and improving quality of life in patients with gliomas. However, the efficacy of monotherapy is limited. Carmustine combined with Temozolomide may have better efficacy in the treatment of gliomas, but the feasibility and safety still need to be further explored. This study provides data on the efficacy and safety of the two in the treatment of glioma, thus providing a theoretical basis.

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