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Effect of Goal-directed Fluid Therapy on Postoperative Cognitive Dysfunction in Elderly Patients Undergoing Combined Lingual and Cervical Radical Surgery

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Abstract

Background: The intraoperative rehydration technique known as the effect of Goal-Directed Fluid Therapy (GDFT), which is guided by the dynamic monitoring of volume responsiveness, has received a lot of attention recently. According to a meta-analysis by Bene, GDFT can maintain intraoperative hemodynamic stability, which lowers the incidence of postoperative complications and reduces stay at the intensive care unit.

Objectives: This study aimed to determine how GDFT affected elderly patients who underwent combined lingual and cervical radical surgery after an operation for postoperative cognitive dysfunction (POCD).

Methods: This interventional study was conducted between December 2021 and December 2022 in a medical center affiliated with Fujian Medical University on people undergoing radical neck and tongue surgery for tongue cancer. The samples (n=36) were selected using an availability sampling method and randomly divided into conventional fluid therapy (the Non-GDFT, n=18) and GDFT (n=18) groups. The Non-GDFT group was hydrated normally during anesthesia. A continuous infusion of 8 mL/(kg/h) of compounded sodium chloride was administered to the GDFT group to maintain basal hydration volume during the operation. Before and following surgery, Montreal Cognitive Assessment Scale scores were completed, arterial blood lactate values and bilateral cerebral oxygen saturation levels were measured at various times following the stabilization of anesthesia, and the levels of interleukin 6 (IL-6) and S100 protein in venous blood were calculated.

Results: The Non-GDFT group had a higher incidence of POCD than the GDFT group, the GDFT group had significantly lower levels of IL-6 and S100 than the Non-GDFT group, the GDFT group had significantly lower levels of serum lactate than the Non-GDFT group. The GDFT group experienced significantly lower rates of intraoperative hypotensive and intraoperative low rSO_2 events than the Non-GDFT group, and this difference was statistically significant ($P<0.05$).

Conclusion: Assuring the balance of cerebral oxygen supply and demand, lowering the production of inflammatory mediators, and successfully reducing the incidence of POCD are all possible benefits of GDFT.

Keywords: Enhanced recovery after surgery, Fluid therapy, Radical surgery, Goal-directed fluid therapy, Postoperative cognitive dysfunction

1. Background

To achieve hemodynamic parameters in patients, fluids are used or combined with inotropes and vasopressors (1). The treatment strategy in cancer patients plays a considerable role in the course of the disease and the patient's life (2, 3). One of the appropriate strategies and measures in the treatment of cancer patients, especially after surgery, is fluid management after surgery (4). Numerous studies are currently being conducted on the management of treatment in cancer patients to choose the best treatment method (5, 6).

The previous methods for fluid therapy that caused complications in patients are currently being tried to reduce both the complications of the operation and the duration of hospitalization in patients (7, 8). One of these methods is the therapeutic method of goal-directed fluid therapy (GDFT) (9, 10). The intraoperative rehydration technique known as GDFT, which is guided by dynamic monitoring of volume responsiveness, has received a lot of attention recently (11). According to a meta-analysis by Bene (12), GDFT can maintain intraoperative hemodynamic stability, which lowers the incidence of postoperative complications and reduces stay in the intensive care unit.

Postoperative cognitive dysfunction (POCD) refers to a condition where patients experience a decline in cognitive function following surgery. The condition can manifest as problems with memory, concentration, and attention, as well as difficulty in processing information and performing mental tasks (13, 14). The exact mechanisms underlying POCD are not fully understood; however, several factors may contribute to its development. These include anesthesia usage, inflammation, oxidative stress, and altered blood flow to the brain (15, 16). Dehydration can harm cognitive performance by decreasing oxygen delivery to the brain, influencing cerebral blood flow, and changing the equilibrium of neurotransmitters. Dehydration has also been linked to a decrease in working memory, focus, and response time (17). The findings of a study in a large sample of elderly patients (18) demonstrated that the incidence of POCD was 25.8% one week after the surgery and 9.9% three months later. It has been found that POCD can lengthen hospitalization and increase mortality (19), with a high incidence in the elderly (20).

The above results highlight the importance of therapeutic fluids during anesthesia. Due to the limited studies on this topic on people undergoing radical lingual and cervical surgery, this study aimed to determine if GDFT could reduce the incidence and severity of POCD in such patients. The study results would provide valuable insights into the potential benefits of GDFT in reducing POCD in elderly patients undergoing radical lingual and cervical surgery.

3. Methods

3.1. Study design and participants

This interventional study was conducted between December 2021 and December 2022 in a medical center affiliated with Fujian Medical University, China. The statistical population was selected based on the availability sampling method (Consolidated Standards of Reporting Trials [CONSORT] algorithm). In total, 36 patients between the ages of 60 and 80 years, who underwent combined radical neck and tongue surgery for tongue cancer, were randomized into two groups, using a randomized numerical table. Therefore, they were divided into conventional liquid therapy (Non-GDFT, n=18) and GDFT (n=18) groups.

The inclusion criteria were being at the age range of 60-80 years, undergoing elective combined tongue and neck radical surgery, being classified as American Society of Anesthesiologists (ASA) I-II, having a body mass index (BMI) of < 28 kg/m^2, having a preoperative hematocrit of > 0.35, and being able to communicate effectively with the physician. On the other hand, the exclusion criteria were having chronic diseases of various systems (e.g., hypertension, coronary heart disease, and diabetes mellitus), cardiac arrhythmias, a history of mental or neurological diseases or family history, and liver and kidney dysfunction; receiving antidepressants, analgesics, and sleeping pills; and having a Preoperative Montreal Cognitive Assessment Scale (MoCA) score of ≤ 13 for illiterate patients, a score of ≤ 19 for those with 1-6 years of education, and a score of ≤ 24 for those with > 7 years of education.

3.2. Pre-anesthesia preparation

Both groups of patients routinely fasted and went without eating or drinking for 8 h before the surgery. A FloTrac/Vigileo system was used to continuously monitor the heart rate, oxygen saturation, invasive arterial blood pressure, mean arterial pressure, cardiac output/cardiac index, stroke volume/speed index, stroke volume variation (SVV), and other indicators. A cerebral oxygen saturation meter continuously measured the bilateral cerebral oxygen saturation (rSO_2).

3.3. Induction and maintenance of anesthesia

In neither group, preoperative medication was given. Anesthesia was induced with sufentanil 0.3 μg/kg, propofol 2 mg/kg, and cisatracurium 0.3 mg/kg, which were injected slowly intravenously in sequence, and the trachea was intubated with the assistance of video laryngoscope. The tidal volume was 8 mL/kg, and mechanical ventilation was performed with an inspiration-to-expiration ratio of 1:1.5 and a respiratory rate of 10-14 breaths/min. The respiratory rate was adjusted according to the partial pressure of end-expiratory carbon dioxide to maintain a respiratory rate of 35-45 mmHg and an intraoperative airway pressure of less than 25 cmH_2O. The concentration of sevoflurane was 2%-4% and 2L oxygen mixed with 1:1 air was inhaled, and the depth of anesthesia was adjusted to maintain the Bispectral Index (BIS) value between 45 and 55. Cisatracurium 0.15 mg/(kg. h) was continuously pumped intravenously during the operation and stopped 30 min before the end of the operation.

3.4. Intraoperative fluid therapy

The non-GDFT group was routinely rehydrated according to the Expert Consensus on Fluid Therapy during Anesthesia (2014) (21, 22). A continuous infusion of 8 mL/(kg. h) of compounded sodium chloride was administered to the GDFT group to maintain the intraoperative basal rehydration volume; and the GDFT protocol was monitored by the FloTrac/Vigileo system based on SVV and SV, with a target SVV of 9% to 13%. Fluid volume expansion was performed when the measured SVV was > 13% (for 3 min) or when the previous rehydration test was positive (SV rose to >10%). The fluid augmentation protocol was 200 mL of succinyl gelatin injection (Glaxo), which was administered over 15 min (23). All patients were kept warm with a thermal blanket and a continuous heating device to keep the nasopharyngeal temperature at ≥ 36.0°C. Transfusion was performed when the bleeding volume was > 25% of the blood volume or Hct < 25%.

3.5. Monitoring indicators

General information: The patients were visited 1 day before the surgery, and their basic information was collected, including age, gender, height, weight, BMI, years of education, ASA classification, and preoperative Hb level. The MoCA score was assessed by the same trained physician on 1 day before the surgery (D1) and days 3 (D2) and 7 (D3) after the operation for all enrolled patients. MoCA has been used as a highly sensitive tool for the early diagnosis of mild cognitive impairment (MCI) since 2000. MoCA is widely used in clinical settings (24). One point was added if the number of years of education was ≤ 12 years. A drop of one standard deviation from the baseline score can diagnose POCD. The concentrations of interleukin 6 (IL-6) and S100β protein were measured by the enzyme-linked immunosorbent assay on D1, D2, and D3. Hemodynamics: The arterial blood lactate and partial pressure of oxygen were recorded 5 min before the start of surgery (T0), at the beginning of surgery (T1), 1 h after the start of surgery (T2), 2 h after the start of surgery (T3), 3 h after the start of surgery (T4) and at the end of surgery (T5) after the stabilization of anesthesia. The number of intraoperative fluids, blood products, blood, and urine loss, and the duration of surgery were also recorded. Postoperative complications: The complications, including nausea, vomiting, respiratory tract infection, incisional infection, and other related complications within 7 days after the operation and the number of days of hospitalization were recorded.

3.6. Statistical analysis

Data were analyzed using SPSS 24.0 statistical software. Normally distributed measures were expressed as mean standard deviation, and the t-test was used to compare general information between groups. Analyses of variance with two-factor repeated measures were used for comparison between groups. The Chi-square test was utilized for the comparison of statistical data. A p-value of < 0.05 was considered a statistically significant difference.

4. Results

Data were completed for 36 of the 40 patients, 18 in each group. The mean age scores of the participants in the GDFT and Non-GDFT groups were 57.28 ± 10.04 and 58.89 ± 8.80 years, respectively, and the two groups had no significant difference in average age. Regarding gender distribution of patients in two groups, in the GDFT group, 12 (66%) were men and 6 (34%) were women, whereas in the Non-GDFT group, 5 (27%) were men and 13 (73%) were women; therefore, the two groups had no significant difference in terms of gender distribution. No difference was observed between the mean BMI and the duration of education in the two groups. The status of ASA (I/II) in two groups showed that in the GDFT group, 5 participants were in class I and 13 participants in class II, while in the Non-GDFT group 9, participants were in classes I and II each; there was no significant difference between the two groups in this regard. The duration of surgery in the GDFT and Non-GDFT groups was 354.72 ± 99.33 min and 365.56 ± 102.45 minutes, respectively, which was not significantly different in (Table 1).

Table 1. Comparison of general information between two groups of patients

Group	GDFT group	Non-GDFT group	P-value
Age (years)	57.28±10.04	58.89±8.80	0.612*
Gender (M/F)	12 (66%) m, 6 (34%) f	5 (27%) 13 (73%)	0.471**
BMI (kg/m²)	22.06±1.67	22.38±1.81	0.551*
Years of education	9.78±2.16	10.33±1.88	0.416*
ASA (I/II)	4/14	9/9	0.087**
Surgery time (min)	354.72±99.33	365.56±102.45	0.749*

*T-test, **Chi-square test

GDFT: Goal-directed fluid therapy, BMI: Body mass index, ASA: American Society of Anesthesiologists

Statistics of POCD events: At D2, the incidence of POCD was higher in Group C than in Group G (61.11% vs 27.78%; P<0.05). On D3, the incidence of POCD was higher in Group C than in Group G (44.44% vs 11.11%; P<0.05) (Table 2).

Table 2. Statistical analysis of POCD in the two groups

Indicators	GDFT group (n=28)		Non-GDFT group (n=28)		P-value*
	Number of cases	Occurrence rate	Number of cases	Occurrence rate	
D2POCD event	5 (28%)	27.78%	11 (61%)	61.11%	0.044
D3POCD event	2 (11%)	11.11%	8 (44%)	44.44%	0.026

*Chi-square test

GDFT: Goal-directed fluid therapy

Comparison of IL-6 levels: Serum IL-6 levels in both groups peaked at time point T2 and gradually decreased at time points T3 and T4, whereas serum IL-6 levels in Group G decreased significantly; the difference in serum IL-6 levels between the two groups was statistically significant (F=39.512, P<0.001). Serum IL-6 levels were different between the two groups at different time points (F=406.004, P<0.001), there was a relationship between group and time (F=7.887, P=0.008), and the changes of serum IL-6 levels over time were different between the two groups (Table 4, Figures 1-3).

Comparison of S100β levels: Compared with the Non-GDFT group, the serum S100β levels in the GDFT group decreased significantly, and the difference in serum S100β levels between the two groups was statistically significant (F=57.568, P<0.001). The serum S100β levels in the two groups were different at different time points (F=427.104, P≤0.001),

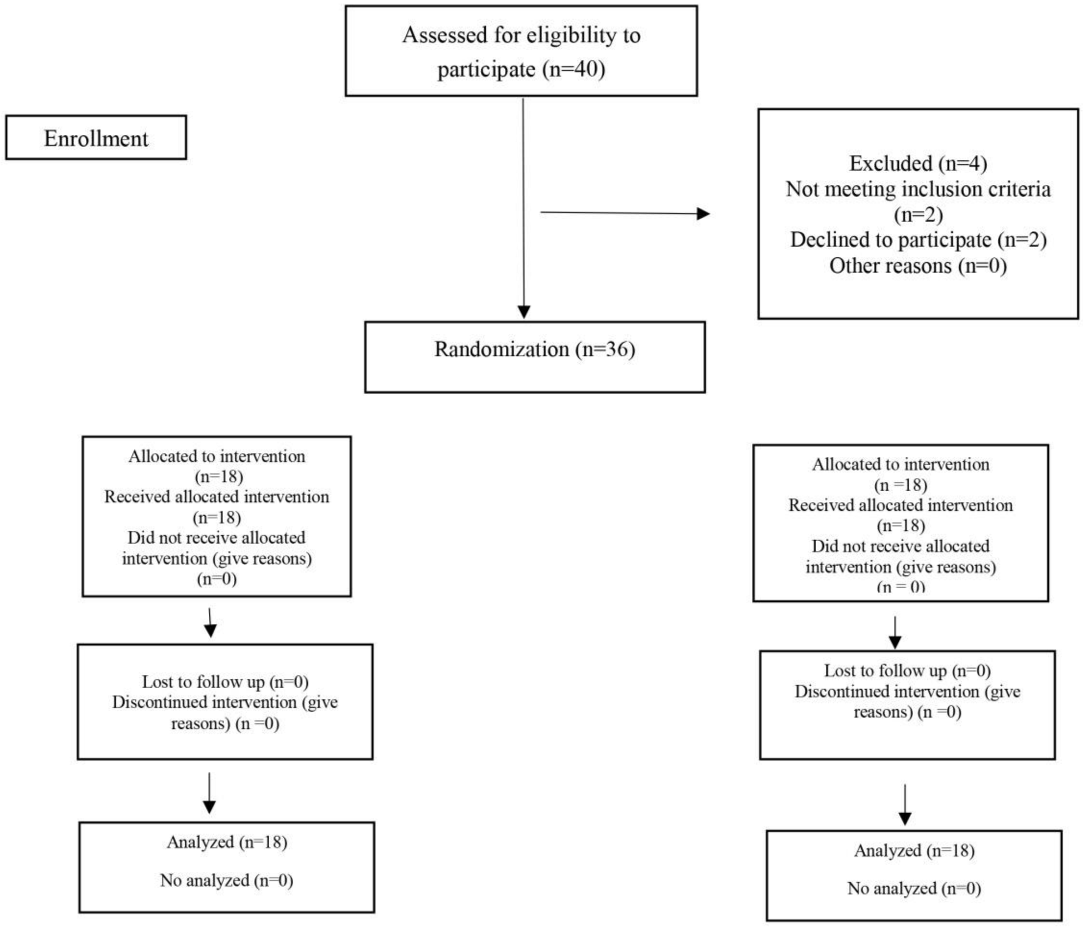

Figure 1. CONSORT algorithm

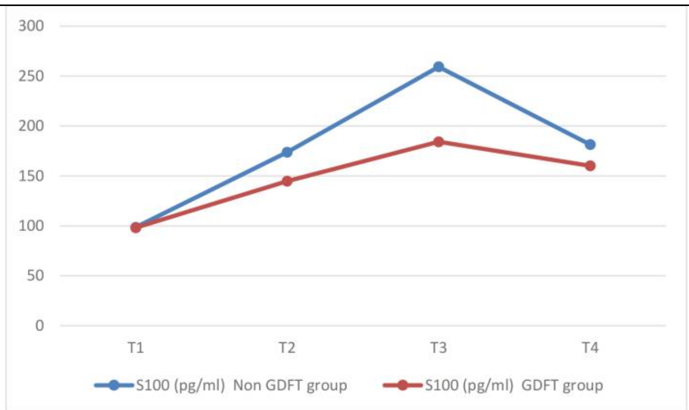

Figure 2. Data of S100 in two groups of patients at different time points

rising to a peak at time point T3 and decreasing at time point T4. There was a relationship between group and time (F=26.239, P<0.001), and the changes in serum S100β levels over time were not the same in the two groups (Table 4, Figures 2, 3).

The results of intraoperative biochemical indices showed that the serum lactate level in the GDFT group was significantly lower than that in the Non-GDFT group, and the difference in Lac between the two groups was statistically significant (F=11.415, P=0.002); the Lac levels in the two groups were different at different time points (F=8.336, P<0.001). There was no relationship between the arterial Lac levels of the two groups in terms of group and time (Tables 3, 4).

At 3 time points after the surgical opening, rSO_2 was significantly higher in the GDFT group than in the Non-GDFT group. The difference in rSO_2 between the two groups was statistically significant (F=648, P=0.014), and the rSO_2 in the two groups was

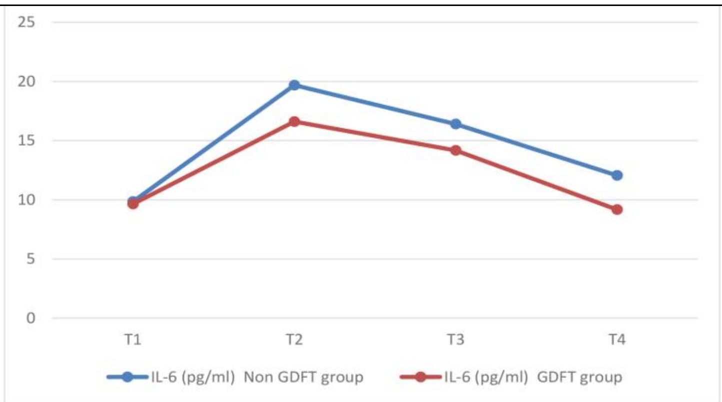

Figure 3. Data of IL-6 in two groups of patients at different time points

Table 3. Data of lactate in two groups of patients at different time points

Indicators	Group	H1	H2	H3	H4
Lactate (mmol/L)	Non-GDFT group	1.46±0.38	1.47±0.33	1.66±0.37	1.80±0.36
	GDFT group	1.63±0.29	1.78±0.24	1.98±0.42	2.09±0.44
rSO_2 (%)	Non-GDFT group	68.00±4.27	67.06±5.62	67.00±4.64	68.89±3.71
	GDFT group	67.72±4.94	64.94±4.22	62.78±4. 19	61.67±3.22

*Two-way repeated measures ANOVA
(Note: H1: 15 min after stabilization of anesthesia induction; H2: at the beginning of the surgery; H3: 3 h after the beginning of the surgery; H4: at the end of the surgery)
rSO_2: Regional cerebral oxygen saturation

Table 4. Results of repeated measures ANOVA of lactate content, rSO_2, IL-6, and S100β

Indicators	Time		Group		Time*Group	
	F	P-value*	F	P-value*	F	P-value*
Lactate (mmol/L)	8.336	0.001	11.415	0.002	0.810	0.498
rSO_2 (%)	12.061	0.001	6.648	0.014	11.177	<0.001
IL-6 (pg/mL)	406.044	0.001	39.512	0.001	13.697	0.001
S100β (pg/mL)	427.104	0.001	57.568	0.001	26.239	0.001

*Post hoc test (Tukey's test)
rSO_2: Regional cerebral oxygen saturation, IL-6: Interleukin 6

different at different time points ($F=12.061$; $P<0.001$). It was revealed that rSO_2 in the GDFT group decreased slightly at T2 and T3 and then gradually increased at T4, while rSO_2 in the Non-GDFT group gradually decreased at T2, T3, and T4; there was a relationship between rSO_2 in the two groups and time ($F=11.177$, $P<0.001$). There was an interaction between rSO_2 groups and time ($F=11.177$, $P=0.001$) (Tables 3, 4).

Intraoperative fluid intake and output statistics showed the total fluid intake in the GDFT group was significantly higher than that in the Non-GDFT group; however, there was no statistical difference in urine volume (Table 5).

Table 5. Fluid intake and outflow of patients during the perioperative period

Group	GDFT group (n=18)	Non-GDFT group(n=18)	P-Value*
Total inflow (mL)	3277.78±662.04	3872.22±814.43	0.037
Total outflow (mL)	450.00±258.96	486. 11±229.32	0.654

*Independent sample t-test
GDFT: Goal-directed fluid therapy

Statistics of other indicators: The incidence of intraoperative hypotensive events in the GDFT group was significantly lower than that in the Non-GDFT group, and this difference was statistically significant ($P<0.05$). The incidence of intraoperative low rSO_2 events in the GDFT group was lower than that in the Non-GDFT group; nevertheless, the difference was not statistically significant. Compared with the Non-GDFT group, the incidence of postoperative nausea and vomiting decreased significantly in the GDFT group, and the difference in the incidence of postoperative malignant heart vomiting between the two groups was statistically significant ($P<0.05$). However, the difference in the incidence of the remaining complications and the total number of hospital days was not statistically significant (Tables 6, 7).

5. Discussion

This study aimed to determine how GDFT affected elderly patients who underwent combined radical lingual and cervical surgery after surgery for cognitive dysfunction (POCD). It was found that the Non-GDFT group had a higher incidence of POCD than the GDFT group, the GDFT group had lower IL-6 and S100 levels than the Non-GDFT group, and the

Table 6. Patients with intraoperative hypotension, low rSO_2 events, and postoperative complications (n=18)

Indicators	GDFT group (n=18)		Non-GDFT group (n=18)		P-value*
	Number of cases	Occurrence rate	Number of cases	Occurrence rate	
Intraoperative hypotension events	2 (11%)	11.11%	8 (44%)	44.44%	0.030
Intraoperative low rSO_2 events	2 (11%)	11.11%	5 (28%)	27.78%	0.201
Nausea and vomiting	3 (17%)	16.67%	9 (50%)	50.00%	0.038
Delirium	3 (17%)	16.67%	8 (44%)	44.44%	0.073
Postoperative hypotension	0	0.00	0	0.00	1.000
Lung infection	2 (11%)	11.11%	7 (38%)	38.89%	0.061
Infection of incision	1 (5.5%)	5.56%	2 (11%)	11.11%	0.500

*Chi-square test
GDFT: Goal-directed fluid therapy, rSO_2: Regional cerebral oxygen saturation

Table 7. Comparison of hospital stay of patients (n=18)

Group	GDFT group (n=18)	Non-GDFT group(n=18)	P-Value*
Hospitalization days	26.78±2.75	27.67±2.56	0.324

*Independent sample t-test
GDFT: Goal-directed fluid therapy

GDFT group had lower serum lactate levels. The results demonstrated that GDFT improves cognitive function in patients. Ensuring the balance of cerebral oxygen supply and demand, reducing the production of inflammatory mediators, and successfully reducing the incidence of POCD were all shown to be the possible benefits of GDFT.

The findings of studies have shown (25) that the Chinese version of the MoCA is an accurate cognitive screening scale for elderly people in China because the MoCA score has a high sensitivity in predicting MCI (26) and Chinese elderly people typically have a low level of education. The Chinese version of the MoCA was used in this study to evaluate patients' postoperative cognitive status (25). The incidence of POCD in the experimental group was significantly lower than that in the control group one week after the surgery in this study, and the findings were consistent with those of related studies conducted both domestically and abroad, indicating that the GDFT intervention significantly decreased the cognitive impairment of postoperative patients with radical tongue cancer.

The pathogenesis of POCD is still unknown. The blood-brain barrier is damaged as a result of the release of tumor necrosis factor and other stimuli brought on by surgical trauma. Mononuclear macrophages are activated and release IL-6, which passes through the blood-brain barrier and mediates the inflammatory response, impairing memory (27). S100 protein is abundant in brain glial cells and is released into the blood and cerebrospinal fluid when brain damage occurs (28). The close connection between IL-6 and S100 and the inflammatory response of brain tissue has been demonstrated in prior studies on POCD (22, 29). In the current study, serum levels of IL-6 and S100 in the experimental group were significantly lower than those in the control group, providing further evidence that GDFT intervention can reduce the inflammation response.

A meta-analysis study conducted by Virág et al. (10), aimed to compare GDFT with Non-GDFT in surgery. The main outcomes included the length of hospital stay, time to first gas and stool, intraoperative fluid and vasopressor requirements, serum lactate level, and urine output. The results of the mentioned study indicated that GDFT, apart from reducing the length of hospital stay, decreased the need to wear a vasopressor and, consistent with the results of the current study, improved cognitive function in patients.

One of the important components of care in surgery is managing the patient's fluids after surgery. Factors such as age, length of surgery, severe blood loss during surgery, and the prone position may affect the administration of intraoperative fluids. A systematic review study, by Ongaigui et al. (25), was conducted to investigate fluid therapy after surgery. The results, in line with those of the present study, showed that GDFT had a direct effect on the cognitive improvement of patients and caused cognitive improvement, although other effects of GDFT should be further investigated.

Lactate is an end product of the glycolytic pathway, produced by anaerobic metabolism, and can be used to assess tissue perfusion (30). In recent years, GDFT has been widely accepted and applied in clinical practices to maintain perioperative hemodynamic stability. In this study, patients receiving GDFT intervention had smoother rSO_2 values than those receiving the conventional infusion, and the absolute value difference between the two groups gradually grew over time. The arterial blood lactate level in Group G was significantly lower than that in Group C, and intraoperative rSO_2 monitoring revealed that patients receiving GDFT intervention had smoother rSO_2 values than those receiving the conventional infusion. The total intraoperative inflow in Group G was significantly higher than that in Group C, even though there was no statistical difference between the two groups, and the total outflow did not differ statistically.

Previous studies have reported that intraoperative hypotensive events are closely related to the occurrence of postoperative POCD; accordingly, the incidence of early POCD increases with the duration of hypotension (22, 31). In this study, the incidence of intraoperative hypotensive events in the experimental group was significantly lower than that in the experimental group, and the patients with GDFT intervention had more stable hemodynamic changes and fewer postoperative complications.

5.1. Limitations

One of the limitations of the study was related to the small sample size. Since the present study was conducted in only one treatment center, this can be mentioned as the other limitation of the current study. In further studies, it is recommended to investigate the effect of other factors on the cognitive performance of patients.

6. Conclusion

In elderly patients undergoing combined lingual and cervical radical surgery, GDFT can effectively improve intraoperative microcirculatory perfusion, ensure the balance of oxygen supply and demand, reduce the production of inflammatory mediators, and maintain hemodynamic stability, which can successfully decrease the incidence of POCD with few intraoperative and postoperative complications.

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None.

Footnotes

Authors' contributions: Liang FQ designed the review and analyzed and interpreted the data. Liang FQ and Fu JJ drafted the manuscript. Liang FQ critically revised the manuscript.

Conflicts of interest: The authors declare that there is no conflict of interest.

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Ethical considerations: This study was reviewed and approved by the Institutional Ethical Review Board of the First Affiliated Hospital, Fujian Medical University (No. 2018-130). Written informed consent was obtained from the patients for publication of this report and any data.

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