

Effects of General Anesthesia Combined with Epidural Anesthesia on Cognitive Dysfunction and Inflammatory Markers of Patients after Surgery for Esophageal Cancer: A Randomised Controlled Trial

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ABSTRACT

Objective: To evaluate the impact of general anesthesia (GA) combined with epidural anesthesia (GAEA) on postoperative cognitive dysfunction (POCD) and inflammatory markers in patients with esophageal cancer (EC).

Study Design: A randomised controlled trial.

Place and Duration of Study: Department of Anesthesiology, Traditional Chinese Medicine Hospital of Southwest Medical University, Luzhou, Sichuan Province, China, from August 2019 to April 2020.

Methodology: SPSS was used to randomly divide 142 cases into two groups, namely: the GA (n=71) and GAEA (n=71) categories. 128 candidates were used in this study. Cognitive function and the levels of interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis markers α (TNF- α) in serum were evaluated at baseline, 1, 3 and 7 days after operation by Montreal Cognitive Assessment (MoCA) and enzyme-linked immunosorbent assay (ELISA), respectively. Pearson correlation analysis was used to assess the interrelationships between MoCA score and inflammatory markers levels.

Results: Compared to the GA group (n=64), the GAEA category (n=64) showed significantly higher MoCA score on 1 day and 3 days postoperatively (all p <0.05). IL-6, IL-8 and TNF- α in the GA group were significantly increased on 1, 3 and 7 days after surgery (all p <0.05). Pearson correlation analysis indicated that the three inflammatory markers were inversely correlated with cognitive function score (all p <0.05). The postoperative adverse events between the two groups were comparable (all p >0.05).

Conclusion: Combining general and epidural anesthesia may reduce the incidence of POCD in patients undergoing esophagectomy by suppressing inflammatory response.

Key Words: General anesthesia, Epidural anesthesia, Esophageal cancer, Postoperative cognitive dysfunction, Inflammatory markers.

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INTRODUCTION

Esophageal cancer (EC) is the eighth most prevalent malignant human cancer globally and has the sixth worst prognosis, because it is often diagnosed after it has advanced or metastasised.¹ Treatment of EC involves surgery, radiotherapy, neoadjuvant chemoradiotherapy (CRT) and immunotherapy.²

Notably, the complicated mediastinal anatomy needs rigorous operation technique, appropriate anesthetic regimen and superior management during post-op period.² Unfortunately, postoperative cognitive dysfunction (POCD), severe systemic inflammatory reactions and anastomotic hemorrhage, influence patient recovery and clinical outcomes, especially in elderly patients.³

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POCD is a category of postoperative central nervous system dysfunction, including cerebral death, stroke and elusive neurologic signs with neuropsychological illness.⁴ Compelling evidence confirms that POCD is related to surgery, the intraoperative anesthetic, the stress response, inflammatory markers and immune system dysfunction.⁵ Previous clinical researches also showed that different anesthetic methods and narcotic drugs may affect POCD.⁶

Inflammatory cytokines are closely related to the occurrence and development of POCD.⁷ Inflammatory biomarkers C-reactive protein (CRP) and IL-6 were relevant to POCD after cardiac surgery.⁷ Kappa opioid receptor agonists could improve POCD in rats *via* inhibiting IL-6 β , IL-6 and TNF- α .⁸ Furthermore, it is becoming increasingly recognised that appropriate anesthesia can reduce the inflammatory response, stress response, postoperative opioid use and various postoperative complications.⁵ However, little information exists on the appropriate form of anesthesia that can be used to avoid POCD during esophagectomy for EC.

The purpose of this trial was to investigate the effect of combining general anesthesia and epidural anesthesia on POCD in patients undergoing esophagectomy and to explore possible mechanisms.

METHODOLOGY

The randomised, controlled trial was approved by Ethics Review Board at Traditional Chinese Medicine Hospital, Southwest Medical University. All patients signed the informed consent before enrollment in the study. The study recruited 142 patients with EC from the hospital, between August 2019 and April 2020. Thereafter, patients were allocated to two intervention groups randomly by SPSS 24.0.

Inclusion criteria were age 18 to 80 years, weight 45 to 80 kgs, elective first-time esophagectomy, neither radiotherapy or chemotherapy history, patients with EC without having any other comorbidities, and preoperative MoCA score of > 15 points. Exclusion criteria were psychiatric or neurological disease, alcohol abuse or drug dependence history, severe cardiovascular diseases, and autoimmune or metabolic diseases.

Firstly, before the induction of anesthesia, patients in the GAEA group were received epidural anesthesia. Epidural puncture *via* the clearance between T7-8 was performed. The catheter was inserted to a depth of 3.5cm and lidocaine (1%, 4 ml) was injected into the space. After 5 to 10 minutes, patients with a good level of analgesia and no adverse reactions, subsequently received intermittent injection of 0.375% ropivacaine (0.1 ml/Kg/h). The control group did not need this procedure. Routine induction of anesthesia involved the use of midazolam (0.05 mg/Kg), propofol (1.5 mg/Kg), sufentanyl (0.4-0.6 ug/Kg) and cisatracurium (0.15 mg/Kg), in all patients. After successful anesthesia, double lumen tube was inserted after visual location using a laryngoscope.

The intermittent positive pressure ventilation settings included tidal volume of 8 to 10 ml/Kg, ventilation frequency of 10 to 12 times/minute, and expiratory/inspiratory ratio of 1:2. Anesthesia was maintained through consecutive intravenous infusion of propofol (4-12mg /Kg/h), remifentanyl (12-60 ug/Kg/h), and cisatracurium (0.1 mg/Kg/h).⁹ The electrocardiogram, heart rate, arterial blood pressure, peripheral capillary oxygen saturation, and end-tidal partial pressure of carbon dioxide were surveillanced. Bispectral index was maintained at 40 to 60. The

administration of all the anesthetics was presided over by physicians (with at least 10 years working experience) with the title of deputy senior or higher. Team members who were blind to the allocation completed the interventions.

The Montreal Cognitive Assessment (MoCA) was used to evaluate memory, naming, visuo-spatial and executive functions, language, attention, abstraction and orientation at baseline, 1st, 3rd and 7th days after the surgery. The serum levels of IL-6, IL-8 and TNF- α at the above timepoints were gauged by Enzyme-linked immunosorbent assay (ELISA). Postoperative infection, hoarse voice, pruritus, reintubation, and reoperation were assessed.

All statistical analyses were conducted using the GraphPad 6.0 and SPSS 24.0. Data were presented as mean \pm standard deviation or case and percentage. Student's t-test was used to evaluate differences between two groups. Paired sample t-test was applied to assess differences in MoCA score and inflammatory markers levels at baseline, day 1, 3 and 7 after the surgery. Chi-square test or Fisher's Exact test was utilised to calculate differences in qualitative data. Pearson correlation analysis was utilised for handling the interrelationships between data. Differences were regarded as statistically significant at $p < 0.05$.

RESULTS

142 individuals were randomly divided into the GA and GAEA groups. Group GA (n=71) were prepared for receiving general anesthesia while group GAEA (n=71) were intended to receive general anesthesia plus epidural anesthesia. Eight operations were cancelled (5 in group GA, and 3 in group GAEA). 134 patients underwent the surgery, 6 patients were lost to follow-up after surgery (2 in group GA, and 4 in group GAEA). Finally, 128 participants finished the study (Figure 1).

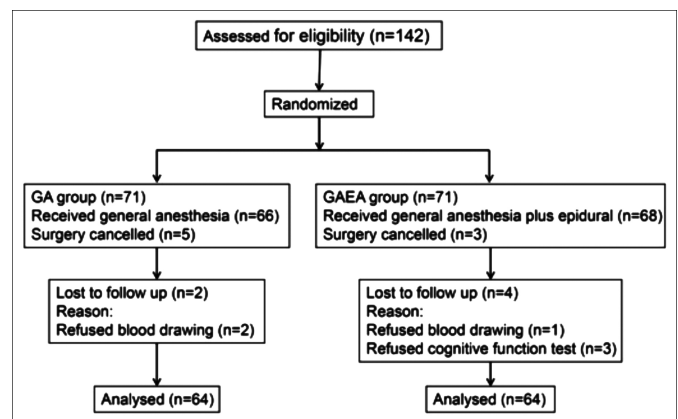


Figure 1: Data flow diagram.

There were no significant discrepancies in baseline demographic, cognitive test results and clinical characteristics between the groups (age 66.70 ± 5.86 vs. 66.58 ± 5.33 years, $p=0.900$; male: 51 (79.7%) vs. 50 (78.1%), $p=0.828$; education over 12 years-7 (10.9%) vs. 6 (9.4%), $p=0.770$; body mass index (BMI)- 23.04 ± 1.27 vs. 22.73 ± 1.81 kg/m², $p=0.263$; diabetes- 12 (18.8%) vs. 9 (14.1%), $p=0.474$; MoCA score: 28.44 ± 1.59 vs. 27.94 ± 1.38 , $p=0.060$; anesthesia time- 261.4

± 66.51 vs. 282.6 ± 64.80 minutes, $p=0.071$; operation time: 227.6 ± 63.98 vs. 245.5 ± 60.87 minutes, $p=0.106$; intraoperative blood loss: 207.4 ± 50.12 vs. 214.2 ± 44.57 ml, $p=0.415$, in the GA and GAEA groups, respectively.

Table I: Comparison of IL-6 levels (x \pm sd) IL-6(pg/ml).

Group	Baseline	1 day after surgery	3 days after surgery	7 days after surgery
All patients (n=128)	70.69 \pm 17.46	148.53 \pm 23.61	130.31 \pm 18.44	95.60 \pm 21.91
GA(n=64)	72.17 \pm 15.23	158.30 \pm 17.19	133.66 \pm 16.05	106.10 \pm 13.91
GAEA(n=64)	69.21 \pm 19.45	138.70 \pm 25.16	127.0 \pm 20.13	85.09 \pm 23.46
*P		<0.001	<0.001	<0.001
P	0.340	<0.001	0.039	<0.001

*P: compared with the data from all patients at baseline; P: compared with group GA.

Table II: Comparison of IL-8 levels (x \pm sd) IL-8 (μ g/L).

Group	Baseline	1 day after surgery	3 days after surgery	7 days after surgery
All patients (n=128)	9.57 \pm 1.17	20.24 \pm 1.76	18.12 \pm 1.81	12.55 \pm 3.82
GA(n=64)	9.77 \pm 1.13	20.86 \pm 1.95	18.84 \pm 1.83	13.51 \pm 3.79
GAEA(n=64)	9.37 \pm 1.18	19.62 \pm 1.29	17.41 \pm 1.48	11.59 \pm 3.63
*P		<0.001	<0.001	<0.001
P	0.055	<0.001	<0.001	0.004

*P: compared with the data from all patients at baseline; P: compared with group GA.

Table III: Comparisons of TNF- α levels (x \pm sd) TNF- α (pg/ml).

Group	Baseline	1 day after surgery	3 days after surgery	7 days after surgery
All patients (n=128)	49.83 \pm 4.83	93.20 \pm 9.79	82.29 \pm 6.73	67.63 \pm 9.25
GA(n=64)	50.67 \pm 4.21	95.91 \pm 5.76	83.67 \pm 5.16	71.64 \pm 7.07
GAEA(n=64)	49.00 \pm 5.27	90.49 \pm 12.05	80.91 \pm 7.80	63.61 \pm 9.47
*P		<0.001	<0.001	<0.001
P	0.051	0.002	0.020	<0.001

*P: compared with the data from all patients at baseline; P: compared with group GA.

Compared with MoCA score at preoperation, MoCA score on the 1st and 3rd days after surgery were distinctly reduced (28.19 ± 1.50 vs. 26.25 ± 1.69 , $p<0.001$; and 28.19 ± 1.50 vs. 27.62 ± 1.77 , $p=0.007$, respectively). No noteworthy difference of MoCA score was seen between preoperation and 7 days after operation (27.94 ± 1.16 , $p=0.144$). The score in group GA was dramatically lower than those in group GAEA on 1 and 3 days after surgery (1 day: 25.86 ± 1.49 vs. 26.64 ± 1.79 , $p=0.008$; and day 3: 27.22 ± 1.84 vs. 28.02 ± 1.61 , $p=0.010$). The two groups had no remarkable discrepancy in the MoCA score, seven days after surgery (27.91 ± 1.26 vs.

27.97 ± 1.05 , $p=0.761$). The occurrence of POCD was significantly higher in group GA than that of group GAEA on the 1st and 3rd days after surgery (1 day: 21 (32.8%) vs. 8 (12.5%), $p=0.006$; and 3 days: 14 (21.9%) vs. 3 (4.7%), $p=0.004$). There were no visible differences in the incidence of POCD at baseline and 7 days postoperatively between the two groups (preoperation: 2 (3.1%) vs. 1 (1.6%), $p>0.999$; and day 7: 2 (3.1%) vs. 0 (0.0%), $p=0.496$).

Visuo-spatial and executive functions, attention and orientation at postoperative day 1 and days 3 were significantly lower in group GA than those in group GAEA (visuo-spatial and executive functions: 4.36 ± 0.65 vs. 4.63 ± 0.49 , $p=0.010$; attention: 4.50 ± 1.51 vs. 5.02 ± 0.98 , $p=0.024$; orientation at postoperative day 1: 5.27 ± 0.67 vs. 5.61 ± 0.55 , $p=0.002$; visuo-spatial and executive functions: 4.61 ± 0.58 vs. 4.88 ± 0.33 , $p=0.002$; attention: 4.94 ± 1.21 vs. 5.42 ± 1.04 , $p=0.016$; and orientation at postoperative days 3: 5.25 ± 0.84 vs. 5.63 ± 0.49 , $p=0.003$). Memory score was 4.14 ± 0.77 and 3.94 ± 0.91 ($p=0.175$) at 1 day; and 4.89 ± 0.36 and 4.81 ± 0.39 ($p=0.244$) at 3 days postoperatively in group GA and GAEA, respectively. Naming score was 2.97 ± 0.18 and 2.91 ± 0.29 ($p=0.147$) at 1 day; and 2.84 ± 0.37 and 2.75 ± 0.44 ($p=0.190$) at 3 days postoperatively in group GA and GAEA, respectively. Language score in the GA and GAEA groups were 2.77 ± 0.43 and 2.70 ± 0.46 ($p=0.427$), respectively on the 1st day after surgery and 2.80 ± 0.41 and 2.67 ± 0.47 ($p=0.111$), respectively on the 3rd day post-operation. Abstraction score in the GA and GAEA groups were 1.86 ± 0.35 and 1.84 ± 0.44 ($p=0.826$), respectively on the 1st day after surgery and 1.89 ± 0.31 and 1.86 ± 0.35 ($p=0.596$), respectively on the 3rd day post-operation. There were no obvious discrepancies in the above indicators before operation and 7 days after surgery between the two groups (all $p>0.05$). These results suggested that GAEA can reduce the occurrence of POCD by affecting visuo-spatial and executive functions, attention, and orientation rather than memory, naming, language, or abstraction.

The results also showed that the levels of IL-6, IL-8 and TNF- α were higher in all the cases on 1st, 3rd and 7th days after surgery, compared to the preoperative levels, especially in group GA (Tables I to III, all $*p<0.05$). The maximum values of the above inflammatory cytokines were appeared on postoperative day 1. Furthermore, the GAEA group had distinctly lower levels of IL-6, IL-8 and TNF- α on the 1st, 3rd and 7th days postoperation, compared to the GA category (Tables I to III, all $p<0.05$). These data demonstrate that GAEA lower the levels of inflammatory cytokines in patients after surgery.

IL-6 was inversely correlated with MoCA score on postoperative days 1 and 3 ($r=-0.194$, $p=0.028$ and $r=-0.177$, $p=0.046$, respectively). Negative co-relationships were found between IL-8 levels and MoCA score on the 1st and 3rd days after surgery ($r=-0.278$, $p=0.002$ and $r=-0.223$, $p=0.011$, respectively).

There was a negative relationship between TNF- α and MoCA score at the above timepoints ($r=-0.282$, $p=0.001$ and $r=-0.233$, $p=0.008$, respectively).

Next, the authors recorded the postoperative AEs and did not find any distinct difference in the occurrence of postoperative AEs between the two groups (postoperative infection: 6 (9.4%) vs. 5 (7.8%), $p=0.752$; hoarse voice: 2 (3.1%) vs. 3 (4.7%), $p>0.999$; pruritus: 1 (1.6%) vs. 2 (3.1%), $p>0.999$; and reintubation: 0 (0.0%) vs. 1 (1.6%), $p>0.999$, in the GA and GAEA groups, respectively.

DISCUSSION

Patients with esophageal cancer have poor resistance to surgery, and are prone to postoperative complications such as POCD, notably in elderly patients.³ The current study also confirmed that anesthesia is one of the most important factors of POCD.¹⁰ When anesthetic drugs enter the patient's body, they inhibit the central and peripheral nerve conduction function in patients, hence blocking pain sensation.¹¹ However, the residual effects of anesthetics may alter the cognitive abilities of patients by changing the vitality of the central nervous system.¹² General anesthesia is widely used in clinical anesthesia, but general anesthetics often cause thalamus, hippocampus and cortex harm.¹³ Epidural anesthesia has the advantages of causing significant analgesia and has less impact on circulation. However, it has shortcomings such as incomplete block and insufficient muscle relaxation.¹⁴ Therefore, it is important to develop better methods of anesthesia based on the existing anesthetic techniques by exploiting their advantages and circumventing their disadvantages.

The results in this study showed that patients who received GAEA had significantly higher MoCA scores than those who received GA. In addition, GAEA could weaken the incidence of POCD, which is consistent with previous researches.¹⁵ Subsequently, the authors analysed which cognitive functions were improved by GAEA. The findings revealed that patients in the GAEA group had higher visuo-spatial and executive functions, attention and orientation scores, than those in the GA category. However, there were no distinct differences in memory, language, naming and abstraction between the two groups. It is notable that there were no significant correlations between the incidence of postoperative adverse events and the two types of anesthesia. It was, therefore, hypothesised that the decrease in the incidence of POCD may have been related to the decrease in the amount of drugs used during GAEA. A series of studies demonstrate that high-dose anesthetics are related to POCD; and other neurodegenerative diseases support hypothesis of the authors.¹⁶

The present study revealed that IL-6, IL-8 and TNF- α were significantly increased in the two groups, on the 1st, 3rd and 7th days after surgery, relative to the preoperative levels. In addition, the GAEA group had significantly lower levels of the three inflammatory cytokines (IL-6, IL-8 and TNF- α) than the GA cate-

gory, on the 1st, 3rd and 7th days after surgery. The study also compared the correlations between the MoCA score and the serum levels of inflammatory factors after surgery. The present data revealed that the MoCA score was inversely associated with the levels of postoperative inflammatory factors. Overall, these results reveal that GAEA can reduce postoperative inflammatory cytokine levels in patients.

Similar to these findings, emerging evidence shows that inflammatory markers are widely involved in the development and progression of POCD.⁶ For example, CRP and IL-6 were linked to POCD after cardiac surgery.¹⁷ In addition, surgical trauma can induce peripheral inflammatory responses and produce a large number of inflammatory markers.¹⁸ Then, inflammatory cytokines can cross the blood-brain barrier into the central nervous system, induce central inflammatory responses, promote oxidative stress responses, and damage neurons and synapses, leading to the development of POCD.¹⁹ Normal concentrations of IL-6 can protect and repair neurons. On the contrary, excessive concentrations of IL-6 exacerbate the damage of neurons and microglia by affecting plasticity of synaptic and neuronal development.^{20,21} Additionally, IL-8 is an important chemokine but also an effective chemoattractant cytokine and neutrophil activator in inflammatory areas, which can be released by endothelial cells, neutrophils, fibroblasts, monocytes and phagocytes, which in turn induce inflammatory responses.²² Recent studies also showed that TNF- α plays a role in POCD by not only affecting neuronal growth and differentiation but also by exerting an effect on synaptic plasticity.²³

Although the present study uncovered some insightful findings, it had a number of limitations. This was a randomised controlled trial with a small sample size. More research using a larger sample size is, therefore, needed to verify the results. The occurrence of POCD and the levels of inflammatory markers were only investigated at baseline, the 1st, 3rd and 7th days after operation. In the immediate future, the authors intend to conduct a study with a longer follow-up. Few inflammatory cytokines were assessed in this study. Future research should, therefore, will evaluate more inflammatory indicators and stress biomarkers.

CONCLUSION

The study suggests that a combination of general and epidural anesthesia not only reduces the incidence of POCD, but also decreases inflammatory reactions in EC patients after undergoing esophagectomy. Moreover, combining general and epidural anesthesia was shown to be effective in esophagectomy; and is, therefore, worth exploring in clinical practice.

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CONFLICT OF INTEREST:

The authors declared no conflict of interest.

ETHICAL APPROVAL:

This study was approved by Ethics Review Board at Traditional Chinese Medicine Hospital, Southwest Medical University.

PATIENTS' CONSENT:

All participants signed the informed consent before enrollment in the study.

AUTHORS' CONTRIBUTION:

PJ: Collected and analysed data, wrote manuscript.

MJL: Collected data.

AQM: Analysed data.

QL: Searched literature.

YZ: Designed study, agreed to be accountable for all aspects of the work.

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