Journal of Anesthesia and Perioperative Medicine

Original Article

Decreased Cerebral Glucose Metabolism in Elderly Patients with Postoperative Delirium: A Case-Control Study

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Citation: Hao Ma, Yan Liao, Yi Mo, Zu-Rong Li, Qin Liao, Yi-Chun Wang, et al. Decreased Cerebral Glucose Metabolism in Elderly Patients with Postoperative Delirium: A Case-Control Study. *J Anesth Perioper Med* 2017; 4 : 162-8. doi: 10.24015/ JAPM.2017.0056

ABSTRACT

Background: Postoperative delirium (POD) is a common postoperative complication in elderly patients. Previous studies have investigated the risk factors and the methods of prevention and treatment of POD. However, the pathogenesis of POD remains unclear. Here we tried to investigate the relationship between cerebral energy metabolism and POD in elderly patients undergoing surgery.

Methods: We performed a case-control study of elderly patients who underwent major abdominal surgery from January 2011 to December 2011. Cerebral glucose metabolism was detected by positron emission tomography with 18F-fluorodeoxyglucose (18F-FDG-PET) and was evaluated by SUV value. POD was diagnosed according to the Confusion Assessment Method for the ICU (CAM-ICU).

Results: In our case-control study, a total of 2195 patients were admitted to ICU after major abdominal surgery, and 42 of them developed hyperactive POD within 48 h after surgery. POD incidence was 1.91%(42/2195). Ultimately, 13 patients with POD were enrolled in the delirium group from the 42 POD patients ($n = 13$). 13 patients without POD were randomly selected to serve as control group ($n = 13$). No significant differences in demographic data, surgical duration, educational level, and key physiological signs and fasting blood sugar level were found between patients with and without POD ($P > 0.05$, respectively). However, patients with POD displayed lower SUV values in the entire cerebral cortex, particular in parietal, temporal and frontal cortex when compared with patients without POD ($P < 0.05$, respectively).

Conclusion: Elderly patients with POD displayed lower cerebral glucose metabolism in the entire cerebral cortex, suggesting that energy deficit is closely associated with POD in elderly patients. (Funded by the National Natural Science Foundation of China and Hunan Provincial Science and Technology Department of China.)

Postoperative delirium (POD), a common postoperative complication in elderly patients, is characterized by fluctuating levels of consciousness, disorganized thinking, and inattention (1). The key clinic manifestation of POD is a rapid change in quality of consciousness and cognition in a short time (2). POD usually begins during the first 24 h after surgery and mostly disappears within the first 4 days after surgery (2-7). Although the duration of POD is short, it is closely associated with longer hospital stay, greater cognitive impairment, increased postoperative morbidity, mortality, and higher health care costs (1- 8). Thus, the prevention and treatment of POD become one of aims to improve the quality of medical care for elderly patients (1).

Accumulating evidences have shown the multifactorial features of POD's occurrence (1, 2). Reported risk factors include older age, pre-operative cognitive impairment, pre-operative sensory impairment, severe somatic illness, history of transient ischemia or stroke, alcohol misuse, psychoactive drug use, uninary catheterization, electrolyte imbalance, low albumin level, infection, and so on (1, 2). In pathological mechanisms, previous studies have shown that neurotransmitter imbalance, neuroinflammation, physiological stressors, metabolic derangements, electrolyte disorders, and genetic factors all contribute to the occurrence and duration of postoperative delirium (1, 2). However, these pathophysiological mechanisms mainly derived from observational data of blood and cognition (1). The true mechanism underlying delirium remains unclear. Interestingly, Saager et al. found that intraoperative tight glucose control increased the risk of delirium after cardiac surgery, but not its severity, in adult patients, suggesting the changes of energy metabolism affected the occurrence of delirium (9). Chen et al. found low hemoglobin level was associated with the development of delirium after hepatectomy for hepatocellular carcinoma patients (10). Changes of energy- related proteins modulate neuroinflammation, oxidative stress, and cognition (11-20). These suggest that abnormal energy homeostasis is a basic pathological reason for the occurrence and development of POD.

Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) is widely used to detect cerebral glucose metabolism that is closely correlated with cognitive function (21). Therefore, in the study, we detected the cerebral glucose metabolism of elderly patients in POD's state by using FDG-PET. Our data showed that glucose metabolism decreased widely in the POD's brain, particularly in the parietal, temporal and frontal cerebral cortex.

MATERIALS and METHODS

Patient Enrollment and Delirium's Diagnosis

Our study was approved by the Institutional Ethics Committee of the Tumor Hospital of Hunan Province, and informed consent was obtained from each potential subject. Potential participants were recruited from 2195 patients who underwent major abdominal surgery such as gastrectomy, radical rectal cancer surgery, sigmoidectomy, partial hepatectomy for hepatic cancer, radical colectomy, and radical cholecystectomy for gall bladder cancer under general anesthesia at Hunan Province Tumor Hospital from January 2011 to December 2011.

Inclusion criteria were: 1) Age 65-85 years; 2) ASA I- II; and 3) surgical operation time 3- 6 hours. Exclusion criteria were: 1) history of central nervous system diseases; 2) diabetes; 3) abnormal thyroid function; 4) intake of sedatives or anti- depressants; 5) history of brain surgery or family history of psychiatric illnesses; 6) uncooperative patients; 7) language/communication difficulties; 8) hearing difficulties; 9) inability to complete neuropsychological tests due to low education level; and 10) perioperative severe hypertension (systolic blood pressure $\geqslant$ 180mmhg and / or diastolic blood pressure $\geqslant$110mmhg) or severe hypotension (systolic blood pressure <80mmhg) or hypoxemia (arterial oxygen partial pressure < 60mmhg or arterial oxygen saturation <88%).

All the qualified patients were admitted to ICU postoperatively. Postoperative hyperactive delirium was diagnosed according to the Confusion Assessment Method for the ICU (CAM- ICU). A case- control study was performed by matching POD group on sex, age, body weight, height, surgical duration, educational level, key physiological signs and fasting blood sugar level, with an equal number of patients randomly selected from the pool of qualified patients who did not develop POD within 48 h after surgery (No- POD Group, n = 13) to serve as control group.

Patient's Preparation and PET Scan

PET-CT examination was performed during the first 6 hour after delirium occurrence. Prior to PET scan, patient weights and heights were measured. Patients were fasted for 4-6 hours, and all the fluids used were glucose-free to decrease the effects of blood glucose on study results. Fasting blood sugar was measured and considered acceptable only if it was at 4.0-6.5 mmol/L. If fasting blood sugar was higher than 6.5 mmol/L, patients were treated with iv or subQ insulin before the imaging study. Patients were monitored with Philips MP20 monitor and EKG, NIBP, pulse oxygen saturation, respiratory rate, and all the patients received oxygen via nasal cannula at a low flow rate.

Patients were administered 18F- FDF (GE MINI trace spiral accelerating agent TracerLab MXFDG) at 4.4 MBq/Kg (about 0.12 mCi/kg) intravenously, and then rested in supine position for 45 min prior to brain PET/CT scanning. After head was placed well in the head cast, the scanning began. Patient heads were first scanned with CT (8 T spiral CT) at a slice thickness of 3.75 mm, and then scanned with PET scanner (GE Discovery ST 8 PET/CT). Each area was imaged for 3 min. Images from CT and PET were subjected to computerized reconstruction and analysis with a Xeleris workstation.

During the PET- CT examination, no sedatives were administered to prevent interference with glucose metabolism. During PET- CT scan, patients were restrained using bands to ensure their safety.

Image Analysis

PET image visual qualitative analysis:

PET images of different cerebral areas were visually analyzed and compared between the cerebral hemispheres bilaterally in the same patient, between patients in the same group, and between patients of different groups based on image color, intensity and patterns. It was considered positive if the radioactivity level was lower (less bright in color) in a cerebral area than in the contralateral area of the same patient or lower in a cerebral area of delirium patients compared with the same area in patients without delirium. A lower cerebral glucose metabolism was defined only if there were at least two cerebral regions at lower radioactivity level and among the regions with at least two or three consecutive sections of lower radioactivity (22).

PET image semi-quantitative analysis:

Semi- quantitative analysis was performed based on the SUV method. SUV refers to the ratio of radioactivity absorbed by the local tissues compared with the average radioactivity of the whole body. It is an indicator describing radioactive uptake of lesions, and is directly proportional to glucose uptake, which reflects glucose metabolic rate. In the PET system, the average SUV of each region of interest is determined by selecting the appropriate program measuring the areas of interest (22).

Statistical Analysis

Data were analyzed with the SPSS software, version 13.0 (IBM). Student′ s t- test or Wilcoxon Rank- Sum test was used to assess differences in variables between subjects who developed delirium and subjects who did not, according to the distribution of the data. Specifically, group comparisons of the SUV mean values of each region of interest between subjects with delirium and subjects with no delirium were assessed by Student−Newman−Keuls (SNK) method. $P < 0.05$ was considered statistically significant.

RESULTS

During the study period (Jan 2011 to Dec. 2011), a total of 2195 patients were admitted to ICU after major abdominal surgery, and 42 of them (42/2195) developed hyperactive POD within 48 h after surgery. Among the 42 patients, 30 patients were excluded due to unwillingness to undergo PET- CT or failure to finish PET-CT. PET-CT failure primarily reflected participant inability to tolerate the duration of scan. Ultimately, 13 patients were enrolled in the delirium group (n = 13). An equal number of patients were randomly selected from the pool of qualified patients who did not develop POD within 48 h after surgery (No- POD Group, n = 13) to serve as control group.

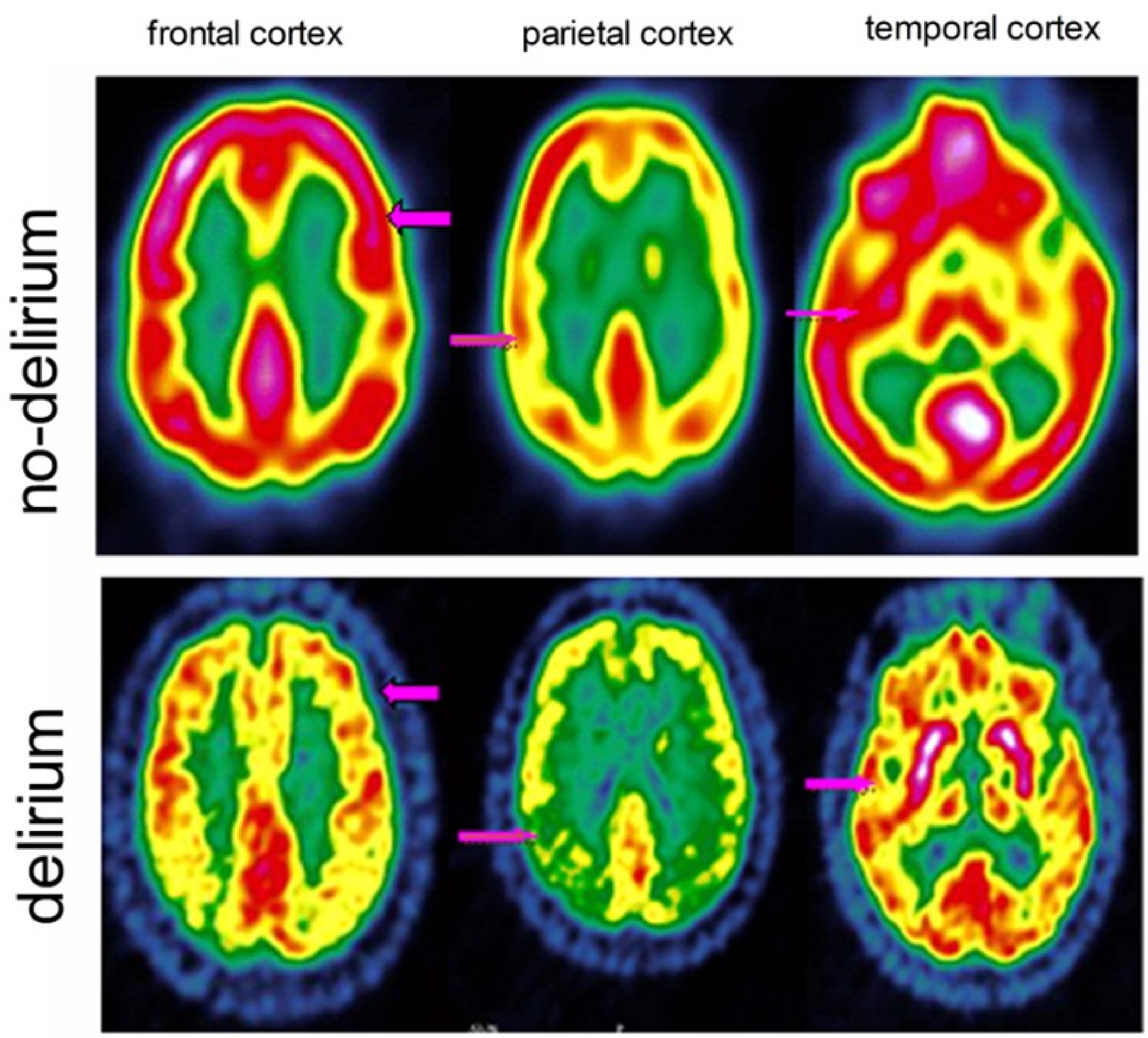

Figure 1. Representative PET/CT Brain Images of Patients with and without Postoperative Delirium. Representative PET/CT brain images of patients with and without postoperative delirium. Images were obtained after patients received intravenous 18F FDG. The different colors represent levels of glucose metabolism, with red denoting the highest, green the lowest, and yellow intermediate levels. The higher intensities of redness suggest higher glucose metabolism levels; and the greener the color, the lower the glucose metabolism.

Demographic data (sex, age, body weight and height), surgical duration, educational level, and key physiological signs and fasting blood sugar level of the 26 Patients before PET/CT scanning were summarized in Table 1 and Table 2. No significant differences in demographic data, surgical duration, educational level, and key physiological signs and fasting blood sugar level were found between patients with and without POD ($P > 0.05$).

Visual analysis and comparison of PET images showed that the intensity of radioactivity was very similar in the cerebral regions bilaterally in the same patient with or without POD. Howev-

Table 1. Patient Demographics and Surgical Data.

Measurement	POD group	No-POD group	T or Z value	P value
Age (year)	75.15 ± 5.86	75.23 ± 4.99	0.036	0.972
Height (m)	1.69 ± 0.06	1.69 ± 0.06	0.067	0.947
Weight (kg)	61.77 ± 4.30	62.01± 5.12	0.166	0.870
Surgical duration (h)	4.00 ± 1.00a	3.50 ± 1.25[a]	0.212[b]	0.832
Educational level (year)	6.46 ± 1.22	6.42 ± 1.12	0.084	0.934

a: not normal distribution, data presented as median, quartile (M, Q); b: Z value.

Table 2. Key Baseline Data before PET/CT Imaging.

Parameters	POD group	No-POD group	t value	P value
MAP (mmHg)	80.85 ± 7.86	79.38 ± 7.86	0.461	0.649
HR(neats/min)	79.23	75.08	1.497	0.147
RR (times/min)	16.85	17.08	0.296	0.770
SPO_2 (%)	98.08	98.31	0.436	0.667
$PETCO_2$ (mmHg)	35.54 Hg (es)	35.77 Hg (es)	0.186	0.854
Blood sugar (mmol/L)	5.17 ± 0.54	5.06 ± 0.58	0.488	0.630

MAP: mean arterial pressure; HR: Heart Rate; RR: respiration rate; SpO_2: Oxygen saturation; $PETCO_2$: end-tidal carbon dioxide pressure.

Table 3. Inter-Group Comparison of SUV Values Across Various Cerebral Regions.

Cerebral lobe	SUV POD group	SUV No-POD group	t value	P value
Parietal, left	4.43±0.85	9.08±1.37	10.409	< 0.001
Parietal, right	4.37±0.77	9.09±0.99	13.542	< 0.001
Temporal, left	4.38±0.69	9.20±1.22	12.418	< 0.001
Temporal, right	4.38±0.68	9.21±1.22	12.470	< 0.001
Frontal, left	4.42± 0.65	9.17± 1.12	13.249	< 0.001
Frontal, right	4.38± 0.73	9.16±1.01	13.889	< 0.001

Table 4. Intra-Group Variation in SUV Values: Right vs. Left Cerebral Lobes.

Group	Cerebral globe	SUV left	SUV right	t value	P value
POD group	Parietal	4.43±0.85	4.37±0.77	0.193	0.848
	Temporal	4.38±0.69	4.38±0.68	0.029	0.977
	Frontal	4.42±0.65	4.38±0.73	0.143	0.888
No-POD group	Parietal	9.08±1.37	9.09±0.99	0.016	0.987
	Temporal	9.20±1.22	9.21±1.22	0.016	0.987
	Frontal	9.17±1.12	9.16±1.01	0.018	0.985

er, patients with POD displayed lower radioactive intensities in the entire cerebral cortex, particular in parietal, temporal and frontal cortex when compared with patients without POD ($P < 0.05$, respectively) (Figure 1). Further quantitative analysis showed that the mean SUV values of the bilateral parietal, temporal and frontal cortex in patients with POD all were obviously lower than that of patients without POD ($P < 0.001$, respectively) (Table 3). In contrast, there was no obvious difference between right and left parietal, temporal and frontal cerebral cortex in same patients ($P > 0.05$, respectively) (Table 4).

DISCUSSION

Our aim is to investigate the relationship between cerebral energy metabolism and POD in aged patients undergoing surgery. We found no significant difference of demographic and baseline clinic characteristics between patients with and without POD. However, patients with POD displayed lower cerebral glucose metabolism in the entire cerebral cortex, particularly in parietal, temporal and frontal cortex when compared with patients without POD. These suggest that energy deficit is closely associated with POD in elderly patients.

Previous studies have shown that neurotransmitter imbalance, neuroinflammation, physiological stressors, metabolic derangements, electrolyte disorders, and genetic factors all contribute to the occurrence and duration of postoperative delirium (1). However, the true mechanism underlying delirium remains unclear. In the study, we tried to detect the cerebral energy metabolism of elderly patients during the process of POD by using 18F- FDG- PET (21). The 18F-FDG is analogous to natural glucose with similar uptake mechanisms (21). Determining 18F-FDG uptake of brain tissue indirectly reflects the rate of cerebral glucose metabolism (21). The more 18F-FDG uptake is, the higher the cerebral glucose metabolism is (22). We found, compared to patients without POD, patients with POD displayed lower cerebral glucose metabolism in the entire cerebral cortex including parietal, temporal and frontal cortex, although there was no significant difference of demographic and baseline clinic characteristics between patients with and without POD. This is in line with the reports of Saager et al. They found that intraoperative tight glucose control increased the risk of delirium after cardiac surgery, but not its severity, in adult patients (9). Peng et al. found that anesthesia/surgery induced obvious reduction of ATP in adult mouse brain after surgery (23). Attenuating the anesthesia/surgery-induced ATP reduction improved the postoperative neurocognitive dysfunction (23). In addition, changes of energy- related proteins modulate neuroinflammation, oxidative stress, and cognition (11-20). These suggest that abnormal energy homeostasis plays a significant role in the occurrence and development of POD.

The incidence of POD varies from 4% to 70%, depending on diagnostic criteria, the characteristics of the study population, and the surgery type (1-8). A higher incidence was reported in the elderly, most medically complex patients after vascular, cardiac, or hip fracture operations (1-8). In our study, the incidence of POD was 1.9% (42/2195) of 2195 patients who underwent major abdominal surgery, lower than the reported incidence of POD. The possible reasons for the lower incidence of POD in our study include two aspects. One is dexmedetomidine's use. A previous study showed that dexmedetomidine administration during surgery reduced the risk of POD (24, 25). In the study, dexmedetomidine was widely used in the recruited patents. The other is that only hyperactive delirium was detected in the study.

In summary, we for the first time detected the cerebral glucose metabolism of elderly patients at the state of POD and found that elderly patients with POD had lower cerebral glucose metabolism. These suggest that abnormal energy homeostasis of brain is closely involved in POD.

This study was supported by grants from the National Natural Science Foundation of China (No.81371216) and Hunan Provincial Science and Technology Department of China(No. 2013SK3054).

The authors have no other potential conflicts of interest for this work.

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