TABLE 1. Characteristics of patients

Variable	Prince of Wales Hospital (n=401)*	Queen Elizabeth Hospital (n=359)*	Tuen Mun Hospital (n=319)*	Princess Margaret Hospital (n=36)*
Age, y	48 (34-58)	46 (33-58)	49 (37-58)	44 (30.8-54.3)
Sex				
Male	319 (79.6)	280 (78)	272 (85.3)	28 (77.8)
Female	82 (20.4)	79 (22)	47 (14.7)	8 (22.2)
Ethnicity				
Asian	398 (99.3)	356 (99.2)	316 (99.1)	36 (100)
Non-Asian	3 (0.7)	3 (0.8)	3 (0.9)	0 (0)
Trauma type				
Non-blunt	54 (13.5)	37 (10.3)	26 (8.2)	2 (5.6)
Blunt	347 (86.5)	322 (89.7)	293 (91.8)	34 (94.4)
Mechanism of injury				
Traffic	170 (42.4)	159 (44.3)	127 (39.8)	21 (58.3)
Fall	129 (32.2)	103 (28.7)	88 (27.6)	11 (30.6)
Penetrating	36 (9)	30 (8.4)	22 (6.9)	2 (5.6)
Burn	17 (4.2)	7 (1.9)	4 (1.3)	0 (0)
Others	49 (12.2)	60 (16.7)	78 (24.5)	2 (5.6)
Work-related injury				
No	259 (64.6)	261 (72.7)	209 (65.5)	34 (94.4)
Yes	142 (35.4)	98 (27.3)	110 (34.5)	2 (5.6)
Psychiatric disease				
No	391 (97.5)	341 (95)	311 (97.5)	34 (94.4)
Yes	10 (2.5)	18 (5)	8 (2.5)	2 (5.6)
Pre-existing comorbidity				
No	287 (71.6)	126 (35.1)	265 (83.1)	18 (50)
Yes	114 (28.4)	233 (64.9)	54 (16.9)	18 (50)
Injury severity score	10 (5.00-20.50)	10 (6.0-21.0)	9 (4.0-17.0)	12 (4.3-18.8)
Abbreviated Injury Scale for head				
<3	264 (65.8)	240 (66.9)	239 (74.9)	26 (72.2)
≥3	137 (34.2)	119 (33.1)	80 (25.1)	10 (27.8)
Operation performed				
No	204 (50.9)	138 (38.4)	151 (47.3)	17 (47.2)
Yes	197 (49.1)	221 (61.6)	168 (52.7)	19 (52.8)
Intensive care unit admission				
No	302 (75.3)	318 (88.6)	245 (76.8)	15 (41.7)
Yes	99 (24.7)	41 (11.4)	74 (23.2)	21 (58.3)
Intensive care unit length of stay	0 (0.00-0.00)	0 (0.0-0.0)	0 (0.0-0.0)	1 (0.0-2.0)
Length of hospital stay	6.4 (3.20-12.10)	10 (5.0-17.0)	9 (5.0-18.0)	8.5 (5.0-19.0)
Extended Glasgow Outcome Scale on discharge				
Good recovery	319 (79.8)	330 (91.9)	273 (85.8)	33 (91.7)
Moderate/severe disability	81 (20.3)	29 (8.1)	45 (14.2)	3 (8.3)
Discharge destination				
Home	316 (78.8)	230 (64.1)	270 (84.6)	29 (80.6)
Non-home	85 (21.2)	129 (35.9)	49 (15.4)	7 (19.4)
30-day mortality				
No	401 (100)	359 (100)	318 (99.7)	36 (100)
Yes	0 (0)	0 (0)	1 (0.3)	0 (0)
No. of years worked	9 (2.0-23.0)	7.5 (2.5-20.0)	8 (2.0-20.0)	6.5 (2.5-20.0)

* Data are presented as mean±standard deviation, median (range) or No. (%) of participants

TABLE 1. (cont'd)

Variable	Prince of Wales Hospital (n=401)*	Queen Elizabeth Hospital (n=359)*	Tuen Mun Hospital (n=319)*	Princess Margaret Hospital (n=36)*
Job nature				
Heavy physical work	242 (63)	250 (70.8)	207 (66.6)	25 (69.4)
Medium physical work	80 (20.8)	57 (16.1)	51 (16.4)	4 (11.1)
Low physical work	62 (16.1)	46 (13)	53 (17)	7 (19.4)
Monthly individual income, HK$				
<20 000	184 (56.4)	177 (51.9)	133 (50.4)	15 (48.4)
≥20 000	142 (43.6)	164 (48.1)	131 (49.6)	16 (51.6)
Education level				
Primary	82 (20.4)	64 (17.9)	59 (18.5)	5 (13.9)
Secondary	241 (60.1)	219 (61.2)	202 (63.3)	20 (55.6)
Post-secondary	78 (19.5)	75 (20.9)	58 (18.2)	11 (30.6)
Living status				
Alone	60 (15)	46 (12.8)	46 (14.4)	7 (19.4)
With family	340 (85)	313 (87.2)	273 (85.6)	29 (80.6)
Compensation				
No	118 (36.8)	88 (26.2)	64 (25.5)	6 (31.6)
Yes	203 (63.2)	248 (73.8)	187 (74.5)	13 (68.4)
Pre-injury physical component summary	55.1±4.7	56.4±4.6	55.7±4	56±3.4
Pre-injury mental component summary	54.6±6.5	54.5±5.2	54.6±6.4	53.6±6
Pre-injury EQ-5D-5L	1±0.1	1±0.1	1±0.1	1±0
1-month extended Glasgow Outcome Scale				
<6	240 (72.9)	286 (85.4)	231 (86.2)	14 (87.5)
≥6	89 (27.1)	49 (14.6)	37 (13.8)	2 (12.5)
1-month physical component summary	38.8±10.9	33±10.4	35.4±10	34.6±11.3
1-month mental component summary	50±10.4	52.6±8.4	48.8±12.3	49.4±14.1
1-month numeric rating scale for pain				
<1	66 (20.9)	50 (16.1)	27 (10.4)	0 (0)
≥1	250 (79.1)	260 (83.9)	233 (89.6)	15 (100)
1-month EQ-5D-5L	0.6±0.3	0.6±0.3	0.5±0.3	0.5±0.3

injury severity score was 10. The Abbreviated Injury Scale score for head was ≥3 in 31% of patients. 54% of patients underwent surgery, and the median length of hospital stay was 8 days. 21% of patients were admitted to intensive care unit. On discharge, 86% of patients reported good recovery and 76% were discharged directly home. 70% patients had applied for compensation after injury.

Overall, 607 (54%) patients had RTW within 12 months of injury. Compared with those who did not RTW, patients who RTW were younger (44 vs 51 years, P<0.001) and had a lower injury severity score (10 vs 11.5, P<0.001), a shorter length of hospital stay (6 vs 11 days, P<0.001), fewer surgery performed (46% vs 65%, P<0.001), and fewer intensive care unit admissions (15% vs 28%, P<0.001).

Patients who RTW had a lower proportion of pre-injury heavy physical work (57% vs 79%, P<0.001), a higher proportion of attaining post-secondary education (28% vs 11%, P<0.001), and a lower proportion of primary level education as highest educational attainment (12% vs 27%, P<0.001). They also had fewer work-related injuries (23% vs 42%, P<0.001) and fewer pre-existing comorbidities (35% vs 41%, P<0.034). With respect to GOSE, 92% of patients who RTW reported good recovery on discharge, whereas 78% of patients who did not RTW had good recovery. In addition, 84% of patients who RTW were discharged home directly, but this was the case in only 66% of patients who did not RTW.

Fewer patients had applied for compensation in the RTW group than in the non-RTW group (63% vs 81%, P<0.001). There were no differences in pre-

TABLE 2. Factors associated with return to work within 1 year of injury

Variable	Univariate analysis		Multivariable analysis			
			Before backward		After backward	
	Odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Age, y						
18-34	1		1			
35-50	0.71 (0.51-0.98)	0.04	0.88 (0.52-1.5)	0.64		
>50	0.47 (0.35-0.64)	<0.001	0.75 (0.42-1.35)	0.34		
Sex						
Female	1					
Male	0.92 (0.69-1.25)	0.60				
Trauma type						
Non-blunt	1					
Blunt	0.99 (0.68-1.45)	0.97				
Mechanism of injury						
Traffic	1		1			
Fall	0.8 (0.61-1.06)	0.13	0.74 (0.43-1.29)	0.29		
Penetrating	0.78 (0.5-1.23)	0.29	0.84 (0.39-1.79)	0.64		
Burn	1.11 (0.51-2.41)	0.80	1.04 (0.28-3.89)	0.96		
Others	0.65 (0.46-0.91)	0.010	0.84 (0.45-1.59)	0.60		
Work-related injury						
No	1		1		1	
Yes	0.43 (0.33-0.55)	<0.001	0.47 (0.28-0.78)	0.003	0.41 (0.28-0.61)	<0.001
Psychiatric disease						
No	1		1			
Yes	0.53 (0.28-1.04)	0.06	1 (0.31-3.28)	1.00		
Pre-existing comorbidity						
No	1		1			
Yes	0.77 (0.6-0.98)	0.030	0.91 (0.61-1.36)	0.65		
Injury severity score	0.97 (0.96-0.98)	<0.001	1 (0.98-1.02)	0.90		
Abbreviated Injury Scale for head						
<3	1					
≥3	1.08 (0.84-1.4)	0.55				
Operation performed						
No	1		1			
Yes	0.45 (0.36-0.58)	<0.001	0.8 (0.51-1.24)	0.31		
Intensive care unit admission						
No	1		1			
Yes	0.46 (0.34-0.61)	<0.001	0.87 (0.51-1.47)	0.5		
Length of hospital stay						
≤8 days	1		1		1	
>8 days	0.35 (0.28-0.45)	<0.001	0.52 (0.34-0.81)	0.004	0.48 (0.33-0.72)	<0.001
Extended Glasgow Outcome Scale on discharge						
Good recovery	1		1			
Moderate/severe disability	0.3 (0.21-0.43)	<0.001	0.86 (0.45-1.64)	0.65		
Discharge destination						
Home	1		1		1	
Non-home	0.36 (0.27-0.48)	<0.001	0.63 (0.38-1.06)	0.08	0.55 (0.35-0.85)	0.007
No. of years worked	0.99 (0.98-1)	0.24	1.01 (0.99-1.03)	0.41		

TABLE 2. (cont'd)

Variable	Univariate analysis		Multivariable analysis			
			Before backward		After backward	
	Odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Job nature						
Heavy physical work	1		1		1	
Medium physical work	2.6 (1.85-3.64)	<0.001	1.81 (1.02-3.21)	0.043	1.86 (1.07-3.24)	0.029
Low physical work	3.13 (2.16-4.53)	<0.001	1.54 (0.81-2.93)	0.19	1.62 (0.87-3.03)	0.13
Monthly individual income, HK$						
<20 000	1					
≥20 000	0.97 (0.75-1.26)	0.84				
Education level						
Primary	1		1		1	
Secondary	2.06 (1.5-2.84)	<0.001	1.57 (0.93-2.67)	0.09	1.61 (1-2.6)	0.05
Post-secondary	5.6 (3.69-8.5)	<0.001	3.63 (1.61-8.19)	0.002	3.91 (1.86-8.25)	<0.001
Living status						
Alone	1		1			
With family	1.49 (1.06-2.08)	0.021	1.32 (0.75-2.34)	0.34		
Compensation						
No	1		1			
Yes	0.42 (0.31-0.57)	<0.001	0.91 (0.58-1.44)	0.70		
Pre-injury physical component summary	1.01 (0.98-1.04)	0.54				
Pre-injury mental component summary	0.98 (0.96-1)	0.11	0.99 (0.96-1.03)	0.65		
Pre-injury EQ-5D-5L	0.44 (0.06-3.11)	0.41				
1-month extended Glasgow Outcome Scale						
<6	1		1		1	
≥6	46.03 (16.91-125.27)	<0.001	41.32 (5.51-309.81)	<0.001	40.22 (5.46-296.39)	<0.001
1-month numeric rating scale for pain						
<1	1		1			
≥1	0.42 (0.28-0.62)	<0.001	1.12 (0.6-2.11)	0.72		
1-month physical component summary						
≤34	1		1		1	
>34	4.01 (3-5.37)	<0.001	1.91 (1.22-3)	0.005	1.86 (1.21-2.88)	0.005
1-month mental component summary						
≤49	1		1		1	
>49	3.13 (2.35-4.17)	<0.001	2.86 (1.9-4.29)	<0.001	2.91 (1.96-4.33)	<0.001
1-month EQ-5D-5L						
≤0.49	1		1		1	
>0.49	5.65 (4.23-7.55)	<0.001	1.51 (0.97-2.37)	0.07	1.5 (0.97-2.31)	0.07

injury health status (physical component summary [PCS] and mental component summary [MCS] of Short Form-12 and the EQ-5D-5L) between the two groups, but the 1-month health status were better in patients who RTW than in those who did not RTW. A higher proportion of patients had GOSE of ≥6 (upper moderate disability) in the RTW group than in the non-RTW group at 12 months after injury (32% vs 1%, P<0.001).

In the multivariable logistic regression analysis, RTW within 12 months of injury were independently associated with non-work-related injury, length of hospital stay of ≤8 days, discharge home directly, non-heavy physical work of job nature, higher educational level, and better 1-month health status (Table 2). A prediction model was established using

TABLE 3. Proposed prediction model for return to work within 12 months of injury

Variables	Score
Non-work-related injury	2
Job nature	
Medium physical work	1.5
Light physical work	1
Education level	
Secondary	1
Post-secondary	3.5
Length of hospital stay of <9 days	2
Discharge directly home	1.5
1-month extended Glasgow Outcome Scale of >5	9
1-month physical component summary of >34	1.5
1-month mental component summary of >49	2.5
1-month EQ-5D-5L of >0.49	1
Score range	**0-24.5**
Area under the receiver operating characteristic curve (95% CI)	**0.850 (0.824-0.875)**

these factors; the area under the receiver operating characteristic curve was 0.850 (95% confidence interval=0.824-0.875) for discriminating RTW and not RTW (Table 3).

Discussion

Predictors for not RTW within 12 months of injury were primary education levels, heavy physical work, work-related injury, length of hospital stay of ≥9 days, not discharge directly home, poorer health-related quality of life measures, and poorer functional outcome at 1 month following injury.

For those who RTW at 12 months, 63% returned to original work at full capacity, 26% returned with reduced work capacity, and 12% changed job nature. In the Victorian State Trauma Registry cohort,[1] 51.6% of respondents had early and sustained RTW, 15.5% had delayed RTW, 13.3% failed RTW, and 19.7% did not RTW. Predictors of delayed and no RTW included having a manual occupation and injuries sustained in motor vehicle crashes. Older age and receiving compensation predicted both failed and no RTW patterns. Severity of injury and treatment factors were not significant predictors for RTW status.

In our prediction model, higher education level and non-manual labour occupations were predictors for RTW, as were length of hospital stay of <9 days, discharge home directly, and 1-month scores of PCS, MCS, EQ-5D-5L, and GOSE. Three-month pain and physical functioning scores have also been suggested to be important.[2]

Although receiving compensation was not a predictor, non-work-related injury was a predictor for RTW in our study, which may remove disincentive for recovery through indirectly receiving compensation and benefits.[3,4]

It is important to routinely collect data relating to longer term outcomes including RTW. Future studies should investigate the role of early dedicated rehabilitation interventions on 1-year RTW rate.

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Effects of electroacupuncture on postoperative cognitive dysfunction: a preclinical study (abridged secondary publication)

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KEY MESSAGES

1. Electroacupuncture reduces cognitive impairment and phosphorylation of tau in a mouse model of postoperative cognitive dysfunction.
2. The protective effects of electroacupuncture are comparable to that of ibuprofen.

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Introduction

Postoperative cognitive dysfunction (POCD) is a common complication following surgery and hospitalisation. After general anaesthesia and surgery, patients may experience impairment in attention, concentration, executive function, memory, visuospatial ability, and psychomotor speed over a period ranging from weeks to years. These changes in cognition can put patients at higher risks of postsurgical complications (eg, misunderstanding wound care and drug treatment instruction).

No specific pathophysiological mechanism can fully explain POCD, owing to its multifactorial nature. Possible explanations include inflammatory responses induced after surgical procedures, excessive neuronal apoptosis, increased oxidative stress, free radical injury, and synaptic changes. Among these, inflammation seems to have a major role in POCD. Both systemic- and neuroinflammation, particularly in the hippocampus, triggered by peripheral surgery trauma or anaesthesia have been proposed for the cognitive deficits. Elevated levels of pro-inflammatory cytokines (such as IL-6, IL-1β, and TNF-α) after surgery may be related to POCD. Morphological changes and activation of microglia after surgery have been reported in preclinical studies. It is proposed that microglia mediate multiple aspects of neuroinflammation and can trigger cognitive dysfunction through multiple signalling pathways.

In our previous study, ibuprofen (a non-steroidal anti-inflammatory drug) could attenuate systemic inflammation and cognitive impairment in mice that had undergone laparotomy. Ibuprofen is commonly used for postoperative pain management, but it can cause gastric bleeding and renal damage and hence not suitable for prolonged use. Non-pharmacological approach for POCD is preferred because of adverse effects of medications, especially in older patients with comorbidities.

Acupuncture and electroacupuncture (EA) have been used to treat neurological and mental disorders. Acupuncture before surgery has been reported to reduce the incidence of POCD and suppress systematic inflammation. This study aims to assess the effects of postoperative EA on cognition and related pathology of mice following laparotomy under general anaesthesia.

Methods

12-week-old male C57BL/6N mice (weighing 25±3 g) were randomly assigned to four groups: sevoflurane alone (control), laparotomy alone, laparotomy + EA, and laparotomy + ibuprofen (positive control). Under anaesthesia with sevoflurane for 20 minutes, a longitudinal midline incision was made in the abdomen. The intestine was exteriorised and generally rubbed for 1 minute and then put back into the abdominal cavity. The muscle layers and skin were then closed and sutured. Analgesic was given for 3 days after laparotomy.

EA treatment was started 2 days after laparotomy to allow sufficient rest. Mice were physically restricted using a custom-made nylon net. Acupuncture needles were inserted horizontally at the Baihui (DU20) and Zusanli (ST36). Electrical stimulation was generated using an EA apparatus set to disperse waves of 1 and 20 Hz. The 7 days and 14 days protocols were used, in which EA treatment lasts for 20 minutes daily for 5 or 12 days, respectively. These time points represent the early and middle postoperative periods. Mice in the control, laparotomy alone, and ibuprofen groups were fixed in place for 20 minutes using similar apparatus but without EA. Mice in the ibuprofen group were fed with ibuprofen (60 mg/kg/day) for 5 or 12 days.

Behavioural changes were assessed using the (1) novel object recognition test for hippocampal-dependent memory, (2) open field test for general locomotor activity and anxiety levels, (3) Y-maze test for associated memory, and (4) puzzle box test for executive functions and cognitive ability.

Mice were euthanised after assessment. The plasma and brain were harvested; the brain was dissected into the frontal cortex and hippocampus. Real-time polymerase chain reaction, western blot analysis, immunohistochemical staining (according to the Accu-OPTIClear protocol), and Milliplex cytokine assays were performed to assess pathological changes in mice.

Results

Electroacupuncture attenuated cognitive impairment induced by laparotomy

To understand the short- and medium-term effects of EA, cognitive performances of mice were assessed at different time points in the 7-day and 14-day protocols. In the Y-maze test, the number of errors in early and medium time points significantly increased in mice in the laparotomy-alone group than in the control group, whereas those received EA made fewer errors than those in the laparotomy-alone group. This suggested an improvement in associated memory. In the novel object recognition test, mice in the laparotomy-alone group displayed reduced ability to differentiate the novel object from the old object, which suggested an impairment in recognition memory, whereas mice that had received EA for 12 days showed significant improvement. In the puzzle box test, mice in the laparotomy-alone group showed significantly impaired problem-solving ability, short-term memory, and long-term memory during the middle postoperative period, but these cognitive changes were attenuated by EA. In most behavioural tests, the effects of EA were similar or slightly worse than that of ibuprofen.

For the general health condition of mice after laparotomy, an immediate weight loss was observed, which persisted for 2 weeks and could not be reversed by EA. The locomotor activity was reflected by the total distance travelled in the arena in the open field test. The anxiety- or depression-like behaviour was reflected by the time spent in outer zone during the open field test. There was no significant difference in the anxiety- or depression-like behaviour between groups. These suggested that the cognitive changes were unlikely to be caused by diminished physical ability or anxiety or depression levels.

Electroacupuncture attenuated laparotomy-induced tau phosphorylation

Tau is an essential protein for maintaining the stability of microtubules. Post-translational modification of tau, such as increased phosphorylation, can occur in pathological situations including Alzheimer disease and results in tau aggregation and generates toxicity. To determine if EA can reduce such pathological changes, we used western blot analysis to assess changes of the tau phosphorylation. Laparotomy induced phosphorylation of tau (AT180, AT8, p-Tau 404, p-Tau 396) in the hippocampus and frontal cortex of mice 14 days after surgery. These changes were partly attenuated by EA. The effects of EA on attenuating tau phosphorylation slightly differed between the hippocampus and the frontal cortex.

Western blot analysis was used to examine any change of tau- and stressed related kinases in the early postoperative period (7 days post-surgery). We found that EA attenuated the activation of GSK3β (at tyrosine 216) and reduced the phosphorylation of JNK after laparotomy in both the hippocampus and the frontal cortex. However, there were no significant changes in the JAK/STAT signalling proteins.

We examined the effects of EA on synaptic proteins, which play key roles in neurotransmission. In the hippocampus, there was no significant change in the levels of synapsin-1, synaptophysin, or NMDAR2B receptor 14 days after laparotomy. EA also did not show any significant effect on the expression of these proteins. In the frontal cortex, a significant reduction of NMDAR2B was found 14 days after laparotomy. However, EA could not reverse this reduction. This suggested that cognitive impairment after laparotomy might not be related to the expression levels of the detected synaptic proteins.

Effects of electroacupuncture on attenuating neuroinflammation

To study the effects of EA on neuroinflammation, we assessed the morphological changes of microglia (detected by Iba-1) and astrocyte (detected by GFAP) in the hippocampus of the mice. There were increased levels of Iba-1 and GFAP in CA1 region of the hippocampus 14 days after laparotomy. Microglia changed their morphology to amoeboid-like shape, with retraction of the fine processes. In astrocytes, the processes showed more ramification (hypertrophy). All these were attenuated in mice that received EA treatment. To determine if cytokines were involved, we examined expression of mRNA for inflammatory cytokines in the hippocampus and frontal cortex 7 days and 14 days after laparotomy. There were no significant changes in the levels of IL-1β, TNF-α, MCP-1, IL-6, IL-10 and IL-8 in the brain in the two time points. However, there were mild yet significant increased levels of TNF-α and IL-10 in the hippocampus 14 days after laparotomy. EA attenuated the increase of IL-10. In the peripheral circulation, there were increased levels of IL-6 and IL-10 in the plasma 7 days after laparotomy. These changes seemed to be attenuated by EA despite not significantly.

Discussion

Postoperative EA could attenuate the cognitive impairment after laparotomy. This effect was not prominent at the early postoperative phrase, in which EA improved the performance of mice in the Y-maze test but not the novel object recognition test. This may be related to the number of EA received before the tests were conducted. When the number of EA treatment was increased in the 14-day protocol, a positive treatment effect of EA was found in both tests. These suggests that a single/few EA treatment is unlikely to attenuate the cognitive impairment. This is not consistent with the finding in a study that a single session of EA during or after surgery is sufficient to reduce the incidence of POCD in patients.[1] It seems that EA before/during surgery provides more beneficial effects than EA after surgery. Our findings cannot be compared directly with those of other animal studies, as different POCD models such as partial hepatectomy or splenectomy are used.[2-4] We believe that laparotomy without removal of any parts of internal organs is a relatively milder surgery. Our data suggested that EA could suppress stress kinases and reduce tau-pathology, but its effect on attenuating neuroinflammation was less prominent.

Conclusion

EA can attenuate cognitive dysfunctions and some neuropathological changes in the brain of mice after laparotomy. The protective effect of EA is slightly lower than that of ibuprofen. EA can attenuate the activation of microglia and astrocyte in the brain. However, other mechanisms, both peripherally and in the brain, may also exist to explain the observed benefits. Postoperative EA can be a viable option for the management of POCD.

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