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Effect of preoperative tropisetron treatment on postoperative cognitive function

A retrospective cohort study

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Abstract

To investigate the effect of preoperative tropisetron treatment on postoperative cognitive function on the basis of patients' Mini-Cog scale scores. In this retrospective cohort study, data were retrieved from the medical record database. This research did not involve concerns with patient safety and violation of their interests, and therefore, no ethical review was required. Depending on tropisetron exposure status, patients were assigned to the exposure group (86 patients) and the non-exposure group (74 patients). Patients in the exposure and non-exposure groups were administered tropisetron (10 mg; intravenously 15 minutes before operation) and other antiemetics, respectively. Data on the patients' demographic characteristics, American society of Anesthesiologists (ASA) classification, comorbid underlying diseases, sleep quality, education level, anesthesia method, duration of fasting, intraoperative blood loss and fluid replacement, intraoperative minimum and maximum systolic blood pressures (SBPs), intraoperative minimum and maximum diastolic blood pressures (DBPs), postoperative Mini-Cog scale (a simple intelligence status assessment scale) score, and postoperative visual analogue scale (VAS) pain score were collected in both the groups. The postoperative Mini-Cog score (as an indicator of cognitive function) and the rate of postoperative cognitive impairment were compared between the exposure and non-exposure groups. A multifactorial logistic regression equation was constructed to analyze the factors associated with impaired cognitive function in the postoperative period. The postoperative cognitive impairment rate in the exposure group was significantly lower than that in the non-exposure group (3.5% vs 16.2%; $P < .05$). Multifactorial logistic regression analysis suggested that tropisetron was a protective factor for postoperative cognitive function, with a statistically significant effect (odds ratio [OR] = 5.04, 95% confidence interval [CI] = 1.31–19.4). Preoperative tropisetron exposure significantly reduces the incidence of postoperative cognitive impairment in patients, and it is a protective factor for postoperative cognitive function.

Abbreviations: ASA = American society of anesthesiologists, CAP = cholinergic anti-inflammatory pathway, CNS = central nervous system, DBP = diastolic blood pressure, PND = perioperative neurocognitive disorders, SBP = systolic blood pressure, VAS = visual analogue scale, α7nAChR = α7 nicotinic acetylcholine receptor.

Keywords: cognitive function, neuroprotection, tropisetron, α7 nicotinic acetylcholine receptor

1. Introduction

Postoperative cognitive impairment is a category of perioperative neurocognitive disorders (PNDs). It mainly manifests as an impairment of cognitive abilities such as learning, memory, and spatial judgment.[1] Its pathogenesis is complex and involves oxidative stress, neuroinflammation and other factors.[2] The α7 nicotinic acetylcholine receptor (α7nAChR) is widely distributed in the central nervous system (CNS), and it is involved in the signal transduction within the cholinergic anti-inflammatory pathway (CAP). This receptor maintains immune homeostasis by regulating multiple immune cells, glial cells and cholinergic neurons and reduces inflammatory responses by inhibiting excessive oxidative stress. It also participates in downstream events such as autophagy and apoptosis, thereby exerting neuroprotective effects.[3] Tropisetron is a 5-hydroxytryptamine3 receptor antagonist that is used to treat perioperative nausea and vomiting, and it also activates the CAP by acting as an α7nAChR agonist.[4] Few studies explored the effect of tropisetron on improving the perioperative cognitive function.[5] Therefore, this study retrospectively analyzed the postoperative cognitive function of patients who were treated with tropisetron preoperatively. The findings of this study could potentially provide a reference for preventing the occurrence of PND.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Materials and methods

2.1. Collection of cases

In this retrospective study, medical records of 160 patients who underwent surgery between January 2020 and August 2022, in our hospital, were retrieved and included. The patients were divided into the exposure (86 patients) and non-exposure (74 patients) groups depending on whether tropisetron was applied preoperatively.

2.2. Inclusion and exclusion criteria

Inclusion criteria: age of 19 to 80 years; ASA classification of I to IV, and absence of a preoperative history of psychiatric/neurological diseases and serious liver, kidney or cardiovascular disease.

Exclusion criteria: presence of incomplete or ambiguous case information; preoperative diagnosis of cognitive dysfunction; and previous history of surgery; and history of brain surgery.

2.3. Indicators

Main indicators: The first indicator was Mini-Cog score. After surgery, patients were tested using the Mini-Cog scale, which includes 2 parts accounting for a total of 5 points: short-term memory test (3 points) – patients were instructed to hear and remember 3 completely unrelated words and repeat them after clock drawing test (CDT); CDT (2 points) – patients were instructed to draw the dial and point to a given time with the hour and minute hands. The lower the scores, the worse the patient's cognitive function.[6,7] The second indicator was cognitive impairment status. A total score of < 3 on the Mini-Cog scale was judged as positive for cognitive impairment.

Secondary indicators: Demographic characteristics of patients in both the groups, including gender, age, height, weight, American society of Anesthesiologists (ASA) classification, combined underlying disease conditions (including diabetes, hypertension, heart disease, and cerebral infarction), sleep quality (classified as poor, fair, and good), education level (including primary school, middle school, university, and postgraduate), anesthesia mode (classified as general, intralesional, and brachial plexus anesthesia), duration of fasting, intraoperative blood loss and fluid replacement, use of vasoactive drugs, intraoperative minimum and maximum systolic blood pressures (SBPs), intraoperative minimum and maximum diastolic blood pressures (DBPs), and postoperative visual analogue scale (VAS) pain score.

2.4. Data processing and statistical analysis

In this study, excel was used for double recording of the data for reconciliation. Statistical analyses were performed using the SPSS 27.0 medical statistics package; normally distributed data are presented as mean ± standard deviation (x ± s), and skewed data are expressed as median (M) with interquartile range (IQR). Two-sample comparisons were performed using the independent samples t-test if conditions of normality and chi-squaredness were satisfied. Otherwise, the rank order test or corrected t-test was used. Categorical data are expressed as examples (%), and χ^2 test was used for comparison between groups. Fisher's exact probability method was used if the minimum theoretical frequency was < 5. Hierarchically ordered categorical variables were converted to metric data according to the purpose of the study. All statistics were tested using a 2-tailed test with an α level of 0.05, with $P < .05$ indicating a statistically significant difference. Multi-factor logistic regression equations were constructed by incorporating factors that differed between the groups and analyzing the factors associated with postoperative cognitive function. $P < .05$ indicates a statistically significant effect.

3. Results

3.1. Baseline characteristics

Hierarchically ordered categorical variables were converted to metric data. There were no statistically significant differences ($P > .05$) in the demographic characteristics (age, sex, height, weight, ASA classification, duration of dietary abstinence, sleep quality, education level, and preoperative underlying diseases) between the exposure and non-exposure groups, which were more consistent at baseline, as shown in Table 1.

3.2. Comparison of intraoperative conditions and postoperative VAS scores

Intraoperative minimum SBP was significantly different between the exposure and non-exposure groups ($P = .006$). The intraoperative minimum DBP was significantly higher ($P = .009$) but the amount of fluid infusion was lower in the exposure group than that in the non-exposure group ($P = .049$). There were no statistically significant differences in the remaining indicators between these groups (Table 2).

3.3. Comparison of cognitive functions

The Mini-Cog scores were significantly higher in the exposure group than in the non-exposure group (4.24 ± 0.76 vs 3.82 ± 1.10; $P = .004$). Furthermore, the rate of cognitive impairment was significantly lower in the exposure group (3 [3.5%] patients) than in the non-exposure group (12 [16.2%] patients) ($P = .006$; Table 3).

Table 1

Comparison of general data.

Observations		Exposed group (n = 80)	Non-exposed group (n = 80)	*t*/*z*/χ^2-value	*P* value
Age (yrs)		49.53 ± 14.27	49.53 ± 14.27	0.22	.83
Gender[n(%)]	Male	52(60.5%)	35(47.3%)	2.78	.095
	Female	34(39.5%)	39(52.7%)		
Height (cm)		167.34 ± 8.82	166.54 ± 7.86	0.22	.82
Weight (kg)		166.54 ± 7.860	70.51 ± 12.33	0.80	.43
ASA classification		1.98 ± .306	2.05 ± .402	1.38	.17
Fasting time (h)		14.37 ± 4.55	15.43 ± 4.542	1.47	.14
Sleep quality		1.23 ± 1.444	1.43 ± .481	0.86	.39
Education level		3.02 ± .891	3.28 ± .031	0.84	.40
Diabetes [n(%)]		5(5.8%)	4(5.4%)	0.01	.91
Heart disease [n(%)]		2(2.3%)	2(2.7%)	0.02	.88
Hypertension [n(%)]		17(19.8%)	20(27%)	1.18	.28
Cerebral infarction [n(%)]		3(3.5%)	4(5.4%)	0.35	.55

ASA = american society of anesthesiologist.

Table 2

Comparison of intraoperative conditions and postoperative visual analogue scale scores.

Observations	Exposed group	Non-exposed group	*t*-value	*P* value
Intraoperative minimum SBP	123.85 ± 13.12	117.78 ± 14.13*	2.81	.006
Intraoperative minimum DBP	70.94 ± 10.70	66.88 ± 8.47*	2.63	.009
Intraoperative maximum SBP	145.43 ± 16.13	144.23 ± 15.30	0.48	.632
Intraoperative maximum DBP	84.66 ± 9.78	82.74 ± 8.74	1.30	.196
Fluid infusion volume	1272.67 ± 467.76	1453.97 ± 682.38*	1.98	.049
Blood loss	194.30 ± 299.02	240.81 ± 301.00	0.98	.330
Minimum PO_2	99.21 ± 1.21	99.26 ± 1.28	0.24	.810
VAS score	1.93 ± 1.06	1.76 ± 0.99	1.06	.29

DBP = diastolic blood pressure, SBP = systolic blood pressure, VAS = visual analogue scale.
* The difference between groups was statistically significant.

Table 3

Comparison of cognitive functions.

Group	Mini-Cog score	Screening positive rate
Exposed group (n = 80)	4.24 ± 0.76	3/86(3.5%)
Non-exposed group (n = 80)	3.82 ± 1.10*	12/74(16.2%)*
t/χ^2-value	2.96	7.58
P value	.004	.006

* The difference between groups was statistically significant.

3.4. Analysis of factors associated with impaired postoperative cognitive function

Based on the above statistical results, a multifactorial logistic regression equation was constructed by including the factors that differed between the 2 groups: intraoperative minimum SBP and DBP, rehydration volume, exposure factors, and status of postoperative cognitive impairment. The effect of tropisetron exposure on postoperative cognitive function was found to be statistically significant (OR = 5.036, 95%CI = 1.30–19.42, $P = .019$), suggesting that tropisetron exposure is an important factor for postoperative cognitive function (Table 4).

4. Discussions

Postoperative cognitive impairment belongs to the category of PND, and the occurrence of PND is associated with a variety of factors. Accumulating evidence is supporting the CNS inflammation hypothesis. This hypothesis suggests that perioperative stimuli cause the release of inflammatory factors, which cross the blood-brain barrier into the CNS. This leads to nerve cell damage, which in turn causes a violent central inflammatory response and disturbance of normal electrical activity of nerves. This affects the synaptic function and leads to the occurrence of PND.[8,9]

α7nAChRs are densely distributed in the CNS and are widely involved in the signaling of the CAP. Dysregulation of α7nAChR-mediated CAP caused by increased anticholinergic activity has been found to be a possible mechanism of impaired neurocognitive function.[3] Perioperative application of anticholinergic drugs may lead to an increased risk for the development of postoperative cognitive impairment, and perioperative application of dopamine is also considered an independent risk factor for the development of postoperative cognitive impairment via a mechanism that may be related to the antagonistic effect of the striatal dopamine system on the cholinergic system.[10] The use of inhaled anesthetics can reduce the central choline release, reduce choline acetyltransferase activity, inhibit postsynaptic nAChRs, cause dysfunction of α7nAChR in the hippocampus and amygdala, and impair postoperative learning and memory functions.[11] Moreover, the stressed state of the body upregulates the activity of acetylcholinesterase, causing the dysfunction of the cholinergic system, including α7nAChR, and affecting the cognitive function of patients.[12]

Tropisetron is a commonly used antiemetic drug, which is a 5-hydroxytryptamine3 receptor antagonist. It also exerts anti-inflammatory and neuroprotective effects through multiple receptor mechanisms, including α7nAchR agonism. It was found that tropisetron selectively activates α7nAchR and mediates CAP to regulate neurotransmitter activity, immune system and other mechanisms to improve the cognitive function in patients with schizophrenia.[13] Tropisetron was also found to increase the expression of serotonin transporter and hippocampal neuron CA1, thereby improving the impairment of cognitive functions, such as spatial memory, caused by brain hypoperfusion.[14] This drug also exerted neuroprotective effects by reducing mitochondrial oxidative stress in the mouse brain and inhibiting neuronal apoptosis and inflammatory responses.[15]

The Mini-Cog is an easy-to-use and easy-to-administer standardized cognitive state screening tool that is commonly used in the examination of cognitive impairment, and its effectiveness is comparable to those of the Montreal Cognitive Assessment and the Mini-Mental State Examination scales, which have obvious clinical applications in the screening of postoperative cognitive impairment.[6,16]

In this study, the Mini-Cog scores of patients in the exposure group were significantly higher than those of patients in the non-exposure group ($P < .05$). The positive cognitive impairment status of patients in the exposure group was significantly lower than that in the non-exposure group ($P < .05$). Moreover, indicators that were significantly different between the 2 groups were used to construct a multivariate logistic regression equation, and it was found that the effect of tropisetron exposure on postoperative cognitive function was statistically significant (OR = 5.036, 95%CI = 1.30–19.42, $P = .019$). The risk of

Table 4

Analysis of factors associated with impaired postoperative cognitive function.

Inclusion factors	B-value	Wald-value	*P* value	OR-value	OR-value 95%CI	
					Lower limit	Upper limit
Exposed factors	1.617	5.510	.019	5.036	1.306	19.426
Intraoperative minimum SBP	0.023	0.842	.359	1.023	0.974	1.075
Intraoperative minimum DBP	–0.021	0.277	.599	0.979	0.904	1.060
Fluid infusion volume	0.001	3.432	.064	1.001	1.000	1.001

DBP = diastolic blood pressure, SBP = systolic blood pressure.

postoperative cognitive impairment in the non-exposure group was on an average 4.036 times higher than that in the exposure group. These results suggest that tropisetron exposure is a protective factor for postoperative cognitive function. The mechanism of action of tropisetron may be through the activation of α7nAchR, which mediates CAP to regulate neurotransmitter activity and the immune system, thereby reducing mitochondrial oxidative stress in the brain and inhibiting neuronal apoptosis and inflammatory responses.

In conclusion, tropisetron can improve postoperative Mini-Cog score and reduce the incidence of postoperative cognitive impairment, which is a protective factor for postoperative cognitive function. This finding must be explored further with an in-depth study. This study has some limitations owing to its retrospective nature and certain factors of bias. Follow-up studies should adopt a randomized controlled design and follow the CONSORT specifications.

Author contributions

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