Review

The Research Progress on Delirium After Peritoneal Pseudomyxoma

Qihong Chen , Xueqin Luo , Chang Liu , Xiuli Bao , Lifei Yu *

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The Research Progress on Delirium After Peritoneal Pseudomyxoma

Qihong Chen, Xueqin Luo, Chang Liu, Xiuli Bao and Lifei Yu *

Aerospace Center Hospital, Beijing, China

* Correspondence: 278483062@qq.com

Abstract

Peritoneal pseudomyxoma (PMP), cytoreductive surgery (CRS) is its most important treatment method. Postoperative delirium (POD) is common in PMP and may be associated with poor prognosis, but there are currently few reports on postoperative delirium in PMP both domestically and internationally, warranting further research. This article reviews the definition, pathogenesis, assessment methods, risk factors, prevention, and treatment measures of postoperative delirium, and analyzes and summarizes them in light of the characteristics of PMP to promote early recognition and optimized treatment of postoperative delirium in PMP, thereby reducing the incidence and improving patient outcomes and quality of life.

Keywords: peritoneal pseudomyxoma surgery; postoperative delirium; risk factors; prevention and treatment

1. Definition and Mechanism of POD

1.1. The Definition of POD

Pseudomyxoma peritonei (PMP) is a rare malignant tumor. The annual incidence is about 1-2 per million [1],It usually originates from the appendix and is characterized by the dissemination of mucinous tumor cells in the abdominal cavity and the characteristic of "accumulation and redistribution" of mucus in the abdominal cavity. It can involve various organs in the abdominal cavity, and the overall prognosis is very poor. Cytoreductive surgery (cytoreductive surgery, CRS) has been proved to significantly improve the 5-year survival rate of PMP patients, and is the current standard treatment for PMP[2,3]。Postoperative delirium (POD) is one of the serious perioperative complications in elderly patients, with an overall incidence of about 18.4%[4],It usually occurs within 0~7 days after surgery and lasts for 1~4 days, which is highly correlated with the poor prognosis of patients. POD prolongs the average hospital stay of patients by 2~3 days and is associated with the mortality rate of 7%~10% within 30 days after surgery[5,6]。Due to the insidious course of PMP, most patients are elderly when they seek medical attention. By the time the tumor is detected, it has often spread extensively throughout the abdominal cavity. Patients generally have poor nutritional status. To ensure adequate tumor reduction, the surgery involves a wide range of areas, requires a prolonged. However, up to now, there are few reports and research data on post-PMP delirium in China and abroad. Thorough study and exploration of the diagnosis, treatment, and prevention of postoperative delirium following PMP (Peritoneal Pneumoperfusion) are essential. By early identification of risk factors and controlling modifiable risk factors, the occurrence of postoperative delirium can be effectively prevented. This not only reduces the duration of patients 'stay in the ICU and hospitalization. Therefore, this paper will elaborate on the research progress of the pathogenesis, evaluation methods, risk factors, prevention and treatment measures of post-PMP delirium, so as to provide reference for subsequent research.

Postoperative delirium (POD) is an acute fluctuating change in mental state following anesthesia and surgery, characterized by acute changes in attention; consciousness and cognitive function[7]。

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Among them, the common characteristics of attention change include the inability to guide, focus, maintain or transfer attention, while cognitive disorder is mainly manifested as memory impairment; orientation abnormalities or perceptual disorders [8]。The fifth edition of (the Diagnostic and Statistical Manual of Mental Disorders, DSM),DSM-5 is the gold standard for delirium diagnosis. All five criteria must be met in the diagnostic criteria,1.Attention and consciousness disorders: attention focusing; Decreased ability to maintain or transfer; Reduced orientation to the environment.2. Acute onset and fluctuating symptoms: Symptoms appear rapidly over a short period of time (a few hours to a few days) and vary in severity within a day.3 Cognitive dysfunction: There is at least one cognitive abnormality such as memory loss; language disorder (e.g., in response to irrelevant questions); and visuospatial perception disorder (e.g., inability to recognize common objects).4. Exclude other diseases or coma: Symptoms cannot be fully explained by pre-existing neurological cognitive disorders (such as dementia) or severe coma.5 There are clear incentives: The cause of delirium (e.g., infection, metabolic disorder, surgical trauma, etc.) needs to be confirmed through medical history; examination or laboratory results. Because the standard diagnosis is complex and cannot be quantified, it is difficult for non-psychiatric professionals without specialized training to master, and it is usually recommended that it be performed by psychiatric professionals. At the same time as diagnosing POD, its severity should be assessed, including the intensity and duration of delirium. According to the clinical manifestations of POD, it is usually divided into high activity type; low activity type and mixed type, respectively accounting for 25%,50% and 25% In clinical practice, high activity is easy to be identified, while low activity is the most common and easy to be missed9。

1.2. The Mechanism of POD Occurrence

POD occurrence is influenced by a variety of factors. First, advanced age is a risk factor for POD. Studies have shown that the risk of postoperative delirium increases with age, with patients over 70 years of age being four times more likely to develop postoperative delirium than younger patients[10]. Secondly, trauma stress caused by surgery is also a key associated risk factor for POD. Studies have found that surgical trauma and intraoperative blood loss can cause peripheral inflammation and damage to the blood-brain barrier, which in turn leads to central anti-inflammatory response and metabolic disorders. It can lead to the release of inflammatory markers in the brain and an imbalance of neurotransmitters, including increased lactic acid response that causes the release of prostaglandin precursor D2 and leads to delirium through synaptic inhibition[11,12] .In addition, abnormal body function and decreased physiological reserves, weakness and depression, sleep disorders, mechanical ventilation and infusion of blood products, pain, intraoperative anesthesia, intraoperative mixed infusion, prolonged bed rest and fasting after surgery are associated with the occurrence of postoperative delirium.

PMP is usually ineffective in traditional treatment due to the dissemination of mucinous tumor in the abdominal cavity, accumulation of a large amount of mucus and involvement of multiple organs. The current standard treatment is to maximize the removal of visible tumors through tumor cell ablation (CRS) and to inhibit the diffuse metastasis of abdominal malignant tumors and postoperative tumor recurrence by combining hyperthermic intraperitoneal peroperative chemotherapy (HIPEC)**Error! Reference source not found.** .During the operation, large amounts of mucus, omentum pie or a large ovary filled with mucus usually occupy the entire abdominal cavity. Moreover, mucinous tumors are implanted in the peritoneum and grow around the organs by compression, which makes the operation difficult, time-consuming and involving a wide range of organs. Compared with conventional surgery in general surgery, CRS takes longer and causes more bleeding. In addition, the rapid decrease of intra-abdominal pressure after the removal of a large amount of accumulated mucus may lead to the instability of circulatory power. According to the data of our center, the average age of PMP patients who received CRS surgery was about 57 years old, among which more than 65 years old accounted for about 23.3%, and more than 70 years old accounted for about 12.8%,The average time of surgical anesthesia was about 8.4h, and the average time of surgical operation was about 7.2h,The maximum amount of abdominal mucin removed by

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surgery was 31000ml, and the maximum amount of intraoperative bleeding was about 5000ml, among which 48.3% of the operators had bleeding volume of more than 1000ml.Therefore, the POD occurrence mechanism of PMP is affected by high risk factors, and other potential high risk factors still need more research to confirm.

2. Evaluation Methods of POD

The assessment of delirium usually includes:

1)Confusion Assessment Method (CAM) is suitable for clinical and research personnel who are not mental health professionals. It is quick and simple, with high specificity but low sensitivity. The patient should be awake and have certain language expression and cooperation ability during the evaluation. CAM was used for delirium assessment before.

2) 3-minute Delirium Diagnostic Scale (3D-CAM).It was improved by Marcantonio et al. in 2014 on the basis of CAM, forming an official mental state assessment tool with the advantages of simple evaluation and high accuracy, which is widely used in emergency departments and delirium screening of the elderly population[15–17].It was improved by Marcantonio et al. in 2014 on the basis of CAM, forming an official mental state assessment tool with the advantages of simple evaluation and high accuracy, which is widely used in emergency departments and delirium screening of the elderly population.

3) The Confusion Assessment Method for ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are widely used in ICU, among which CAM-ICU has higher specificity for the evaluation of medical ICU and mechanical ventilation patients 18.

4) CAM-severity scale (confusion Assessment Method-severity, CAM-S) has strong psychometric characteristics and high predictive efficacy for important clinical outcomes related to delirium 19.

5) Nursing delirium screening scale ,Nu-DESC) :Delirium is generally assessed by nursing staff according to the presence and severity of specific clinical features, and its severity is graded without the cooperation of patients. It has high sensitivity and specificity, and is simple and easy to perform.At present, more assessment scales are being tested and developed. In practice, appropriate scales should be used for delirium assessment according to the specific situation of patients.

For PMP, it is important to detect and accurately assess the occurrence of POD as early as possible. It is recommended to use the 3-minute Delirium Diagnosis Scale (3D-CAM) to accurately and quickly evaluate and diagnose POD.

3. Risk Factors for POD

3.1. Patient-Related Risk Factors

3.1.1. Advanced Age

The study found that advanced age was a risk factor for postoperative delirium 19.The risk of postoperative delirium increases with age. Foreign studies have also found that patients over 65 years of age are more likely to develop POD after surgery, with the risk increasing by 1.15 times for each additional year of age19。Clinical data from our center showed that the age of PMP patients receiving CRS was 67 years or older with POD.

3.1.2. Abnormal Body Function and Decreased Physiological Reserve and Multiple Complications

Tumor consumption can lead to anemia and coagulation dysfunction and imbalance of water, electrolyte and pH balance. Electrolyte disorders can further reduce the stability of cell membranes, which in turn causes dysfunction of vascular endothelium, leading to cerebral cell edema, fatigue, apathy, drowsiness, depression, decreased reactivity and other mental symptoms. Studies have found that advanced age, decreased physiological reserves (cognitive, functional and nutritional),

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multiple comorbidities, drug or alcohol dependence, and genetic factors (such as the ApoE4 genotype) are associated with POD 22.In a retrospective observational study, Li et al. found that advanced age, preoperative arrhythmia, hypoalbuminemia, coagulation dysfunction, history of psychiatric and cognitive disorders, and low surgical Apgar score were independent risk factors for POD in major abdominal surgery**Error! Reference source not found.**. Low hemoglobin or anemia can lead to POD by reducing the level of oxygen in the brain or its ability to store it. The occurrence of POD may be due to surgical stress, which promotes brain metabolic damage and inflammatory response, while hyperglycemia is a risk factor for inducing cellular level and physiological reactive inflammation**Error! Reference source not found.**,Therefore, patients with preoperative diabetes have a high risk of postoperative delirium. A retrospective analysis by Ganai et al. also suggested a correlation between postoperative delirium and hyperglycemia in patients undergoing abdominal surgery**Error! Reference source not found.**.In addition to tumor consumption symptoms, patients with PMP have a huge tumor mass and mucus accumulation in the adominal cavity, which can lead to increased intra-abdominal pressure, affect hemodynamics, further aggravate organ dysfunction, and make it easier for the body to suffer from malnutrition and decreased physiological reserves.

3.1.3. Weakness and Depression

Weakness is an increase in vulnerability and a decrease in the ability to resist stress caused by the decline of physiological cognitive reserves. It is independently related to the increased incidence of POD, and is not affected by age, type of surgery, or POD diagnosis method27.Depression is an independent risk factor for postoperative delirium, and patients with persistent severe depressive episodes before surgery have nearly four times the risk of postoperative delirium28.Affected by the particularity of diseases and personal physiological and psychological factors, most PMP patients have symptoms of weakness and depression.

3.1.4. Dyssomnia

Dyssomnias are closely associated with cognitive dysfunction, depression and dementia, and POD can be caused by mechanisms such as neuroinflammation, changes in neurotransmitter activity, blood-brain barrier, cerebrovascular disease, interruption of brain automatic regulation, sympathetic-vagal imbalance, and interruption of brain bioenergetics29.Many studies have found that dyssomnia is an independent risk factor for delirium in postoperative patients. As a controllable factor, sleep plays a certain role in the prevention and treatment of delirium by regulating postoperative sleep[30–33].PMP patients often have sleep disorders after surgery.

3.2. Risk Factors Related to Surgery

3.2.1. Mechanical Ventilation and Infusion of Blood Products

Smulter et al. found that prolonged mechanical ventilation was associated with an increased incidence of postoperative delirium**Error! Reference source not found.**.The surgical resection range is wide, the trauma area of the surgical area is large, a large amount of bleeding and exudation occur, resulting in a sudden decrease in abdominal pressure and hemodynamic changes, and a large number of blood products and fluids need to be infused during the operation. A review of the literature found that up to 77% of patients undergoing CRS/HIPEC required intraoperative allogeneic blood transfusions, and approximately 37% of patients required more than 6U of allogeneic red blood cells**Error! Reference source not found.**.Li Xiaodong et al. found that intraoperative blood transfusion was associated with POD, and the amount of intraoperative blood transfusion in delirium group was higher than that in non-delirium group**Error! Reference source not found.**.A prospective cohort study by Janssen et al. showed that red blood cell infusion increased the risk of delirium**Error! Reference source not found.**. Wang Yuqiang et al. found that the risk of POD in patients who received allogeneic blood during surgery was 5.650 times higher than that in patients who received autologous blood during surgery**Error! Reference source not found.**. Rugider et al. found that

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platelet transfusion was an independent risk factor for postoperative delirium38.PMP surgery usually takes a long time and mechanical ventilation takes a long time. Studies have shown that long operation and anesthesia time can increase the incidence of postoperative delirium38.

3.2.2. Pain

Pain is prone to stress response, which changes nerve conduction and causes peripheral inflammatory cytokines to migrate to the central nervous system and cause inflammation, which eventually leads to delirium. A study on pain and postoperative delirium showed that age, moderate to severe preoperative resting pain and increased postoperative pain levels were risk factors for delirium44.Pain is a common adverse reaction after PMP.

3.3. Risk Factors Related to Anesthesia

EVERED L A et al. studied 655 high-risk patients undergoing major surgery from 8 centers in 3 countries, and concluded that patients with mild anesthesia had a lower risk of postoperative delirium and cognitive impairment than those with severe anesthesia after major surgery[43];The use of benzodiazepines, anticholinergic drugs and opioids was positively correlated with the incidence of POD44.At present, the bipolar spectrum index (BIS) is used in clinical practice to monitor the depth of anesthesia and avoid excessive anesthesia. It can not only reduce the amount of general anesthetic drugs during surgery, but also accelerate the recovery of patients' cognitive function after surgery, reduce the occurrence of POD, and improve the long-term prognosis of patients. A meta-analysis has shown that anesthesia depth monitoring can significantly reduce the risk of POD44.CRS needs to be performed under general anesthesia, and the use of various anesthetic techniques and anesthetic drugs may be associated with POD.

3.4. Other Risk Factors

Studies have shown that intraoperative mixed infusion and long-term bed rest are risk factors for postoperative delirium[46].Long-term fasting and drinking ban can lead to discomfort such as thirst and anxiety, increase the incidence of postoperative nausea and vomiting, and are closely related to the risk of postoperative delirium**Error! Reference source not found.**.A large amount of fluids and blood products were infused during PMP to effectively ensure the body's needs. After CRS, patients were generally bedridden and fasted for 5-10 days, which could induce POD.

4. Preventive and Therapeutic Measures for POD After PMP Surgery

4.1. Non-Drug Prevention and Treatment

4.1.1. Preoperative Education and Postoperative Treatment Measures

For patients with common risk factors such as advanced age, cognitive impairment, mental illness and dyssomnia before surgery, the knowledge of POD was explained by doctors and nurses before and after surgery to improve the awareness of POD among family members and patients. The medical staff informed the family that POD is a common and short-term acute symptom, and provided information about delirium and postoperative care, listened to the family's voice, solved their doubts, encouraged them to participate in the patient's delirium management, including providing medical history, observing symptom changes, frequent companionship and communication with the patient. Previous studies have shown that preoperative correction of susceptible factors and improvement of physiological function reserve can help reduce the risk of POD**Error! Reference source not found.**.A multicenter randomized clinical trial conducted by Deeken et al.in Germany targeted clinical interventions, such as cognitive training, exercise, companionship, and sleep promotion, for patients aged 70 and older undergoing orthopedic, abdominal, or cardiac surgery. It was confirmed that individualized non-pharmacological

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interventions significantly reduced the incidence of POD and percentage of days of delirium in patients undergoing orthopedic or abdominal surgery49.In a randomized controlled trial, Waszynski et al. used watching family video messages as a non-drug treatment. It was confirmed that this measure can reduce agitation symptoms in patients with hospitalization delirium50.Similarly, other non-drug treatments such as environmental and cognitive behavioral support, music therapy, and massage have been shown to improve the severity and duration of symptoms following POD51.Due to the particularity of PMP disease, our center has strengthened preoperative education for patients with high risk of delirium after surgery, and improved the awareness of POD among family members and patients. After surgery, we have adopted the above individualized non-drug intervention for POD patients, which has achieved significant clinical effect.

4.1.2. Treatment Measures for Abnormal Body Function

For patients with severe nutritional imbalance, water and electrolyte acid-base balance disorder and anemia PMP before surgery, correction should be made as soon as possible, and parenteral nutrition support treatment, reasonable and timely infusion of fluids and blood products should be given. Patients with abnormal coagulation function and hyperglycemia should be treated as soon as possible to achieve the indications for surgery. For patients with high intra-abdominal pressure due to high tumor load before surgery, the head of bed should be raised 30°to 45°before surgery to improve pulmonary ventilation and venous return. Diuretic and nutritional support treatment should be given, and peritoneal puncture catheterization should be performed to drain ascites when necessary. In the postoperative period, we paid close attention to the symptoms, laboratory indicators and imaging results of the above patients. If any abnormality occurs, appropriate treatment should be given as soon as possible to prevent the occurrence of POD in PMP.

4.1.3. Precautions for Surgery and Anesthesia

It is recommended that PMP surgery and CRS and HIPEC be performed in well-experienced centers. Before the start of CRS, the operator should make a comprehensive and detailed assessment of the patient, make a complete plan for the operation content, clarify the scope and method of surgical resection, estimate the operation time and bleeding amount, and make a plan in advance to accurately and effectively grasp the operation time and reduce the duration of mechanical ventilation. When the patient is in good physical condition before surgery, autologous blood should be prepared for use during the procedure to reduce the need for allogeneic blood transfusions. During preoperative and intraoperative anesthesia, avoid using benzodiazepines, anticholinergics, and opioids. Monitor the depth of anesthesia to prevent it from becoming too deep, thereby reducing the amount of general anesthetic required during the operation. Postoperatively, appropriately use analgesics such as ibuprofen, tramadol, and dezocine to minimize postoperative pain and stress responses.

4.1.4. Preventive Measures for Other Risk Factors

The patient's cardiopulmonary and renal function was assessed before and during the operation. During the fasting period, the infusion of fluids was strictly ordered and the type and dose were controlled. It is recommended to adopt goal-directed fluid therapy (GDFT).The so-called GDFT involves real-time monitoring of hemodynamic parameters (such as stroke volume variation, pulse pressure variation rate, and perfusion variability index) to implement personalized fluid therapy. This is combined with vasoactive drugs to optimize the heart's preload, afterload, and vascular tone. This approach maintains effective circulating blood volume, ensures microcirculation perfusion and tissue oxygen supply, and prevents tissue edema. Clinical studies have shown that the use of GDFT can more stably stabilize patients' water, electrolyte and acid-base balance, reduce the incidence of postoperative infection, cause less intestinal dysfunction, promote the recovery of postoperative gastrointestinal function, and shorten the length of hospital stay51;Shorten the preoperative fasting

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and drinking time as far as possible, which can not only reduce the risk of postoperative delirium, but also prevent anesthesia aspiration, and ensure the safe and successful completion of surgery.

4.2. Drug Prevention and Treatment

Confirmed effective drugs are used for early intervention in patients at high risk of POD to reduce the incidence of POD. Girard et al. evaluated the effects of haloperidol and risperidone on treatment of delirium in the ICU, and found that these drugs did not alter the duration of delirium symptoms or patient outcomes54.A number of studies have shown that dexmedetomidine plays an important role in preventing POD. In Li et al. 's study, the use of dexmedetomidine during surgery was found to halve the risk of POD in elderly patients undergoing non-cardiac surgery55.At present, POD patients with PMP in our center often use dexmedetomidine to gradually improve POD symptoms and effectively shorten the duration of POD symptoms. The intervention of other drugs remains to be studied in the future.

5. Outlook

In summary, the occurrence of POD in CRS seriously affects the prognosis of patients and increases their economic, psychological and spiritual pressure. This paper studies the POD occurrence mechanism, evaluation method, risk factors, prevention and treatment measures of PMP to effectively reduce the incidence. However, there are many challenges and uncertainties at present. In addition to adequate clinical practice and laboratory tests, psychiatric imaging is still in the research and development phase; How to optimize the diagnostic tool to quickly and accurately identify POD and risk stratification; The use of drugs for prevention and treatment is controversial and requires new research and development. In the future, the combination of non-drug prevention and drug prevention may become a new direction for postoperative delirium treatment. More clinical trials and prospective clinical studies are urgently needed to determine safe and effective POD prevention methods.

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