

# Intranasal Insulin Combined with Low-Dose Propofol in the Treatment of Postoperative Intractable Delirium: A Case Report and Literature Review

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**Abstract:** *Background:* Currently, postoperative delirium is a common postoperative complication in elderly patients. However, it lacks effective treatment measures, and this case report strives to find a more effective treatment method based on the existing treatment measures. *Objectives:* The aim of this study was to investigate the efficacy of intranasal insulin combined with low-dose propofol in the treatment of refractory delirium. *Methods:* Five days after a 66-year-old woman underwent surgery under general anesthesia, she underwent surgery again under general anesthesia. After the second operation, the patient was sent to the ICU to continue observation. On the second day after entering the ICU, the patient was confused, restless, increased speech, unable to respond correctly, and had aggressive behavior. After the neurologist's treatment was invalid, the anesthesiologist was invited again for consultation. The anesthesiologist evaluated the patient through the RASS scale, CAM-ICU scale and CAM-R scale and found that the patient was currently in a state of delirium. Therefore, it was decided to take TCI target-controlled infusion of propofol, intranasal insulin administration, and dynamic monitoring of the patient's breathing with a microfluidic end-tidal carbon dioxide (PETCO<sub>2</sub>) monitor through a nasal cannula to control the patient's delirium state. *Results:* After 36 hours of treatment, the patient was conscious and quiet, communicated to the point, and had a clear understanding of the surrounding environment. *Conclusion:* Intranasal insulin combined with low-dose propofol can provide reference for the treatment of intractable delirium.

**Keywords:** Intranasal Insulin, Propofol, The Microstream PETCO<sub>2</sub> Monitor Via the Nasal Catheter, Postoperative Delirium

## 1. Introduction

Postoperative delirium (POD) is an acute neuropsychiatric syndrome, generally occurring within 7 days after surgery in elderly patients. The incidence of POD in elderly patients has been reported to be as high as 15% to 62% [1]. The development of POD not only increases mortality at 6 to 12 months after surgery, but can also seriously affect quality of life and health status, prolong the length of hospital stays, increase hospitalization costs, and exert great pressure on society and families [2, 3]. Currently, the main measures for clinical treatment of delirium include basic disease treatment, maintenance of water and electrolyte balance, nutritional

support, mental support, etc [4]. The key to treatment is to end delirium as soon as possible. Commonly used therapeutic drugs include diazepam, droperidol, propofol, etc, which can shorten the time of delirium. Propofol can inhibit the release of norepinephrine from the central nerve synapse after binding to the locus coeruleus alpha 2 receptor, inhibit locus coeruleus discharge and the excitability of the postsynaptic membrane, and has multiple effects such as sedation, hypnosis, easy arousal, and anti-anxiety [5]. Studies have shown that the use of propofol infusion at a lower anesthetic dose is effective in treating refractory delirium [6]. At present, insulin delivery to the brain has become an important treatment target for cognitive disorders associated with abnormal brain energy metabolism. Recent studies [7] have

indicated that intranasal insulin administration can increase the concentration of insulin in the brain and can significantly reduce the production of monocyte chemotactic protein-1; release of inflammatory mediators IL-6, TNF- $\alpha$ , and IL-1 $\beta$ ; stimulation of human microglial cells; and toxicity of microglial cells to neuronal cells, all of which can improve cognitive function and thus exert brain-protective effects. In the early stage, our research [8] has shown that repeated preoperative intranasal administration of insulin prevented the occurrence of delirium after laparoscopic radical gastrointestinal surgery in elderly patients and reduced TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 levels. Based on the above studies, we suspect that intranasal insulin combined with low-dose propofol can enhance the therapeutic effect of postoperative delirium.

## 2. Case Presentation

An elderly female patient was 66 years old, 158CM in height and 66kg in weight. She had a history of hypertension for 3 years, did not take medication regularly, and had poor blood pressure control. The results of the electrocardiogram showed incomplete right bundle branch block and the heart rate was 58 beats/min. The rest of the inspections are nothing special. Because of the cystic dilatation of the common bile duct and choledocholithiasis, she electively underwent the fourth-generation Da Vinci robot-assisted laparoscopic choledochal cyst resection, cholangiojejunostomy, and cholecystectomy under general anesthesia. The patient developed biliary peritonitis due to bile leakage after surgery. On the 5th day after the first operation, the patient underwent emergent exploratory laparotomy, biliary-enteric anastomosis leak repair and abdominal lavage again under general anesthesia. After the second operation, the patient was sent to the ICU to continue observation.

One day after admission to ICU, the patient suddenly had confusion of consciousness, manic anxiety, increased speech, inappropriate answers, aggressive behavior, insufficient understanding of the surrounding environment, evasive behavior and irritable state. Biochemical examination suggested that the patient had serious infection and abnormal liver function. After consultation with a neurologist, the patient was treated with diazepam, haloperidol, and sodium valproate, but the symptoms were not significantly improved. An anesthesiologist was invited to consult again. The anesthesiologist evaluated the patient through the RASS scale, CAM-ICU scale and CAM-R scale and found that the patient was currently in a state of delirium. The anesthesiologist adopted TCI target-controlled infusion of propofol (Plasma effect chamber concentration 0.7 $\mu$ g/ml) combined with insulin intranasal administration until discharge (20U/time, 3 times/day), while using microparameter flow end-tidal carbon dioxide monitor (inhaled oxygen concentration 5L/min) to dynamically monitor the patient's respiratory, so that it is convenient to find respiratory depression in time to intervene. Every 3 hours, the use of propofol shall be suspended, and whether

the patient is in delirium shall be evaluated. After 36 hours of treatment, the patient was conscious and quiet, communicated to the point, and had a clear understanding of the surrounding environment. In addition, the CAM-ICU scale and the CAM-R scale indicated that the patient's delirium state was negative. Biochemical examination showed that the inflammatory related indexes basically returned to normal. The patient was transferred to the general ward after his vital signs stabilized. After 5 days, the patient was discharged safely. When discharged from the hospital, the CAM-ICU scale and the CAM-R scale were used to evaluate the patient again, and the patient's status was negative.

## 3. Discussion

The peritoneum can be contaminated by bile in many ways, causing biliary peritonitis. The commonest is post-cholecystectomy. This is usually due to the division of small bile channels between the gall bladder and liver, imperfect clipping of the cystic duct, residual CBD stones causing raised intra-biliary pressure and inadvertent division of an accessory hepatic duct [9]. In this case, the patient had biliary peritonitis due to a large amount of bile leaking from the anastomosis after cholecystectomy. Bile peritonitis can induce a series of inflammatory reactions that promote release of inflammatory mediators, including TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and C-reactive protein. These mediators are then transported into the brain through passive diffusion and through active transport across the blood-brain barrier, enhancing permeability of the blood-brain barrier and stimulating afferent vagal nerves to activate microglia and astrocytes. Continued microglial activation produces nitric oxide, which causes DNA deamination and neuronal cell death, and increases levels of reactive oxygen species, which cause lipid peroxidation, and proinflammatory cytokines, which endanger the central nervous system and cause neuronal and synaptic dysfunction, triggering POD [10-12]. It is widely accepted that postoperative delirium occurs by the cumulative interactions between predisposing and precipitating factors [13]. In this case, the cause of POD in this patient may be the complementary results between the preoperative risk factors such as advanced age and hypertension and the precipitating factor of postoperative peritonitis.

The previous symptomatic treatment of POD, such as the treatment of underlying diseases, maintaining water and electrolyte balance, supplementing nutrition, strengthening postoperative analgesia, and drug treatments based on droperidol and diazepam, cannot control this state. Increasing the dose will increase the extrapyramidal response and arrhythmia. Propofol takes effect quickly and has a short action time. It mainly plays a sedative and hypnotic role by activating GABA receptor and chloride ion complex. At the same time, it can produce sedative effect by acting on NMDA receptor. GABA receptors and NMDA receptors are involved in the occurrence of this manic state. Therefore, the above

mechanism provides a theoretical basis for propofol in the treatment of delirium [14]. At the same time, studies have shown that low-dose propofol can make patients go through delirium smoothly [15]. However, considering that its sedative effect may cause respiratory depression, we also used the microstream PETCO<sub>2</sub> monitor via the nasal catheter to monitor its respiratory situation in real time and dynamically, so as to facilitate timely intervention. In recent years, intranasal insulin has been used in more and more models due to its role in reducing inflammation and thus exerting brain protection. For example, intranasal insulin can attenuate the anxiety-like behaviors caused by methamphetamine, and significantly reduce the levels of glial cell markers (GFAP and Iba1), TNF- $\alpha$  and IL-6, and the expression of COX-2 and NF- $\kappa$ B molecules related to hippocampal neuroinflammation [16]. In the human immunodeficiency virus (HIV) /acquired immunodeficiency syndrome (AIDS) neurodegeneration model, intranasal insulin therapy can also restore neurobehavioral function by reducing neuroinflammation and neuronal damage [17]. In addition, our previous studies have also shown that intranasal administration of insulin can reduce the occurrence of postoperative delirium in elderly patients by reducing the expression of inflammatory factors [8]. Therefore, we adopted the method of intranasal insulin combined with low-dose propofol to allow intranasal insulin to continue to consolidate and play the role of brain protection after propofol stopped.

## 4. Conclusions

Intranasal insulin combined with low-dose propofol can have positive significance in the treatment of intractable delirium. However, there is still a lack of clinical experience in the treatment of postoperative delirium with intranasal insulin combined with low-dose propofol. After consulting a large number of literatures, we tried to use intranasal insulin combined with low-dose propofol to treat postoperative delirium. Through the treatment of the above cases, we have accumulated certain clinical experience and provided intranasal insulin combined with low-dose propofol to treat postoperative delirium. In the future, we will further carry out clinical trials of intranasal insulin combined with low-dose propofol in the treatment of postoperative delirium, to provide a basis for its wide clinical application.

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