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ORIGINAL RESEARCH

Intranasal Insulin Diminishes Postoperative Delirium and Elevated Osteocalcin and Brain Derived Neurotrophic Factor in Older Patients Undergoing Joint Replacement: A Randomized, Double-Blind, Placebo-Controlled Trial

Mi Yang, Lei Zhou, Ge Long, Xing Liu, Wen Ouyang, Chang Xie, Xi He

Department of Anesthesia, The Third Xiangya Hospital of Central South University, Changsha, People's Republic of China

Correspondence: Xi He, Email hexitougao@163.com

Background: Brain energy metabolism disorders, including glucose utilization disorders and abnormal insulin sensitivity, are linked to the pathogenesis of postoperative delirium. Intranasal insulin has shown significant benefits in improving glucose metabolism, insulin sensitivity and cognitive function. However, its impact on postoperative delirium and insulin sensitivity biomarkers remains unknown.

Aim: This randomized, double-blind, placebo-controlled trial was to evaluate whether intranasal insulin reduces the incidence and severity of postoperative delirium (POD) in older patients undergoing joint replacement, and its effect on insulin sensitivity-related biomarkers.

Methods: 212 older patients (≥65 years) were randomly assigned to receive either 40 IU of intranasal insulin (n=106) or a placebo (n=106) for 8 days. The primary objective was to determine the incidence and severity of POD within 5 days after surgery, estimated using the Confusion Assessment Method (CAM) and the Delirium Rating Scale (DRS)-98. The secondary objective was insulin sensitivity, which was assessed using the homeostasis model Assessment of Insulin Resistance (HOMA-IR) and biomarkers, including total osteocalcin (tOC), uncarboxylated osteocalcin (ucOC), and brain-derived neurotrophic factor (BDNF).

Main Results: Compared to placebo, intranasal insulin significantly reduced the incidence of delirium within 5 days after surgery (8 [8.33%] vs 23 [23.23%], P = 0.004, odds ratio [OR] = 3.33 [95% CI 1.41–7.88]) and the severity of delirium (P<0.001). Intranasal insulin elevated the levels of tOC, ucOC, and BDNF in the CSF on D_0 (all P<0.001) and tOC levels in the plasma on D_0, D_1 and D_3 (all P<0.001). It elevated ucOC levels in the plasma of the insulin group on D_0 but not on D_1 and D_3 (all P<0.001). Intranasal insulin administration reduced the HOMA-IR on D_3 (P=0.002).

Conclusion: Intranasal insulin notably reduced the incidence and severity of POD in older patients undergoing joint replacement, which may be related to the elevation in osteocalcin and BDNF levels.

Trial Registry Numbers: Chinese Clinical Trial Registry (ChiCTR2300068073).

Keywords: intranasal insulin, osteocalcin, postoperative delirium, brain derived neurotrophic factor, older patient

Introduction

Postoperative delirium (POD) is a common and life-threatening complication in older surgical patients, characterized by acute disorders of attention and cognition.[1] With the global population aging and life expectancy increasing, the annual incidence of POD continued to rise.[2] Despite the use of multimodal strategies, including pharmacological and non-pharmacological approaches, the prevention and treatment of POD remain challenging due to limited efficacy and

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significant side effects.[1,3] This underscores the urgent need for safe and effective therapeutic options to address this growing healthcare issue.

Intranasal insulin has emerged as a promising candidate for preventing neurocognitive disorders by reducing neuroinflammation and improving brain glucose metabolism.[4,5] Intranasal drug delivery bypasses the blood-brain barrier, delivering insulin directly to the central nervous system with minimal systemic side effect.[6] Recently, intranasal insulin has shown benefits in the prevention and treatment of perioperative neurocognitive disorders in both animal models[7,8] and clinical studies.[9,10] However, the underlying mechanisms remain uncertain.

The protective effect of intranasal insulin on perioperative neurocognitive disorders is inseparable from improvements in peripheral insulin sensitivity and cognitive function. Intervention with intranasal insulin can improve peripheral insulin sensitivity by promoting glucose uptake and catabolism in tissues and muscles via a specific pathway unclear.[11] Interestingly, studies have shown that osteocalcin signaling in muscles promotes glucose uptake and catabolism, even in insulin deficiency or insulin resistance state.[12,13] Moreover, osteocalcin levels are related to insulin sensitivity and elevated osteocalcin levels contribute to the amelioration of insulin sensitivity.[14] More importantly, osteocalcin, a hormone that tightly links bone metabolism, energy metabolism, and cognitive function, also plays an important role in the regulation of cognitive function.[15] Osteocalcin can cross the blood-brain barrier, accumulate in specific areas of the brain, and participate in cognitive regulation of cognition.[16] It can specifically bind to the Gpr158 receptor in the CA3 region, increase brain-derived neurotrophic factor (BDNF) levels, and is necessary for hippocampal-dependent memory and the prevention of anxiety-like behaviors.[17] Mice lacking osteocalcin showed abnormalities in cognitive function, such as impaired learning and memory, which were alleviated by osteocalcin supplementation.[15] In older patients, low osteocalcin levels are associated with microstructural changes in the brain and worse cognitive performance.[18] However, osteocalcin supplementation reduced age-related cognitive decline in older mice.[19] In brief, insulin signaling can promote increased levels of osteocalcin,[20] and increased osteocalcin appears to improve both insulin sensitivity and cognitive function. Therefore, we hypothesized that intranasal insulin improves cognitive function and peripheral insulin sensitivity by increasing peripheral and central osteocalcin levels, playing an important role in mitigating perioperative neurocognitive decline.

This study aims to explore the effects of intranasal insulin on the incidence and severity of postoperative delirium, peripheral insulin sensitivity, and biomarker levels in older patients undergoing joint replacement, providing new insights into the potential of intranasal insulin as a preventive strategy for perioperative neurocognitive disorders.

Materials and Methods

Registrations, and Ethic

This randomized, double-blind, placebo-controlled clinical trial was conducted at the Third Xiangya Hospital, Central South University. This study was approved by the Ethical Committee of the Third Xiangya Hospital of Central South University (IRB K22051, Chairperson Prof. Zhiying Su, October 20, 2022), and written informed consent was obtained from all participants. The trial was registered prior to patient enrollment in the Chinese Clinical Trial Registry (ChiCTR2300068073, Principal investigator: Mi Yang, Date of registration: February 6, 2023). The study was conducted in accordance with the 2010 Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Participants and Study Design

Recruitment took place between February 10, 2023, and December 30, 2023, at the Third Xiangya Hospital of Central South University, and was stopped for futility in accordance with the Data and Safety Monitoring Board (DSMB). Eligible patients were those aged 65 to 95 years, with American Society of Anesthesiologists (ASA) physical status I to III, scheduled for elective joint replacement surgery under combined epidural anesthesia, and stayed in the hospital after surgery for more than 5 days. Additional inclusion criteria were that the participants must be able to communicate with the researcher and complete the relevant scale assessments (no serious visual impairment or hearing problems). The exclusion criteria were any pre-existing psychiatric (eg depression and schizophrenia) or neurological conditions (eg intracranial tumors), surgery within the past year, a baseline Mini-Mental State Examination (MMSE) score of <

23,[21] or other conditions that the attending physician or investigator deemed inappropriate to participate in the study (the patient had a serious nasal disease that affects the efficacy of intranasal administration). To compare the differences in frailty between the two groups of older patients, a comprehensive geriatric assessment was performed (Supplementary Table 1).

Randomization and Blinding

After providing consent, eligible patients were randomized using a random number generated in a 1:1 ratio on a computer program (SAS 9.2 software) and assigned to receive intranasal sprays in the morning and night with either 40 IU of insulin detemir (1 mL) or placebo (1 mL normal saline) twice a day from the 3rd day before surgery to the 5th day after surgery for 8 days.[22] Human insulin detemir (Levemir; Novo Nordisk, Novo Alle, Denmark) was packaged in nasal spray bottles (Aeropump, Hochheim am Main, Germany) at the Department of Clinical Pharmacy Experimental Center. Equal volumes of normal saline were provided in the same packaging as in the placebo group. The masked drug was provided by a pharmacist who was independent from investigators and clinicians. The randomization results were sequentially sealed in numbered envelopes until the end of the study. In an emergency of clinical work (such as an accident or rapid deterioration of the patient's condition), the professor involved in clinical treatment can immediately demand to see the treatment group status to adjust or interrupt the administration of the study drug to the subject, if necessary. All incidents were recorded in the participants' report files.

Anesthesia Procedures

During the perioperative period, all clinical management procedures followed recognized clinical practice. All patients received combined epidural anesthesia. Lumbar anesthesia drugs are 1.5 mL 1% ropivacaine, 0.025 mg fentanyl, 0.5 mL 10% glucose and 0.5 mL cerebrospinal fluid. Epidural drug supplementation 2 to 3h after the administration of lumbar anesthesia; 4 mL 2% lidocaine was first administered as an experimental dose according to the anesthesia level, and then 5 mL 0.75% ropivacaine injection was added every 1.5 to 2 hours according to the anesthesia level. None of the patients received any preoperative medication (such as atropine or diazepam). Other aspects of management (blood pressure indicators and use of vasoactive drugs) were at the discretion of the attending anesthesiologist. Avoiding the use of medications known to affect cognition (such as benzodiazepines or dexmetropine). All patients were treated with patient-controlled analgesia (PCA). 150 ug sufentanil and 8 mg ondansetron were diluted to 150 mL with normal saline at a rate based on height, weight, and pain threshold. The VAS score of all patients was controlled to ≤3 and the treatment regimen remained the same (all patients were administered intravenous dezocine injection). All patient conditions were recorded in the case report.

Outcome Measures

Measurements of the Incidence and Severity of Postoperative Delirium

The primary outcome was the incidence and severity of postoperative delirium, determined using the Confusion Assessment Method (CAM) and the Delirium Rating Scale-98 (DRS-98).[23] Five days after surgery, the patient was assessed by two trained visitors once a day in the morning and evening for the CAM and visual pain scales, and the Delirium Rating Scale-98 (DRS) was performed to assess the severity of delirium. Delirium was assessed using an experimental delirium evaluator between 8:00 and 10:00 AM and 7:00 and 9:00 PM, and was evaluated twice a day. Possible episodes of delirium outside the assessment time were evaluated by interviewing the patients' companions, ward nurses, and nursing records. The clinical research assistants who performed the delirium assessments in this study were well trained and underwent quality control procedures. The POD was evaluated using the Confusion Assessment Method (CAM). Four clinical criteria were used to diagnose POD: (1) acute onset and fluctuating course of the disease, (2) inattention, (3) confused thinking, and (4) changes in level of consciousness. To define delirium, (1) and (2) must both be satisfied in addition to (3) and/or (4). The severity of the POD is determined using the Delirium Rating Scale-98 (DRS), with higher scores indicating more severe delirium. Patients were divided into postoperative POD (POD) and post-operative delirium-free (non-POD) groups according to whether they developed delirium.

Measurements of Osteocalcin, BDNF, Insulin, Glucose, and Insulin Sensitivity

Peripheral blood was collected from 6 to 8 a.m. on the day before intervention ($D_{baseline}$), the day before surgery (D_0), the first day after surgery (D_1), and the third day after surgery (D_3). The obtained plasma was immediately centrifuged at 3000 rpm for 10 minutes at 4°C. CSF was acquired in the immediate preoperative period during the induction of spinal anesthesia (PREOP). All samples were immediately frozen at −80°C. Enzyme-linked immunosorbent assays were used to measure biomarkers. The concentrations of total osteocalcin (tOC), uncarboxylated osteocalcin (ucOC), brain-derived neurotrophic factor (BDNF), and insulin in plasma and CSF were measured using a solid-phase enzyme-linked immunosorbent assay (ELISA) kit (Jiancheng, Nanjing, China). The glucose concentrations in the plasma and CSF were measured using a glucose assay kit (Jiancheng, Nanjing, China) and the glucose oxidase method. The detection limits of the biomarkers were different, and all the detected results were within the limits (detection limits: BDNF, 1.5625–50ng/mL, tOC, 10–320ng/mL, ucOC, 0.5–16 ng/mL, insulin, 2–64mIU/L). Regarding the repeatability of the ELISA kit, the coefficient of variation was less than 10% both within and between plates.

Insulin sensitivity was estimated using a homeostasis model assessment of insulin resistance (HOMA-IR).[9,24] HOMA-IR was calculated using the following formula: Fasting Insulin × Fasting Glucose/22.5. A baseline HOMA-IR index greater than 2.6 was predefined arbitrarily as insulin resistance. According to our previous study,[10] although intranasal insulin improves insulin sensitivity quickly (within a few hours), the time of significant changes in HOMA-IR is relatively late. Therefore, the detection time of HOMA-IR was selected as the 4th and 7th days after the intervention (ie, at D_0 and D_3).

Statistics

Sample Size. Our previous prospective cohort study showed that the incidence of POD within 5 days in older patients after joint replacement surgery was 23.3%,[25] the sample size calculation used a two-sided design at a significance level of 5% ($\alpha = 0.05$) and a power of 95% ($1\text{-}\beta = 0.95$), assuming an incidence of 23%, and indicated that 106 patients per group would be needed to detect a 60% decrease in the incidence of POD. In total, 106 patients were recruited for each group. After formal review was requested by the data monitoring and ethics committee, the sample size was not revised, because the attrition rate was 10% or less within the anticipated.

For the primary outcome, the difference in delirium incidence between the two groups was analyzed using the chi-square test. The difference in delirium severity was analyzed by comparing the peak DRS values between the two groups using the rank-sum test. For secondary outcomes, the differences in osteocalcin levels and insulin sensitivity between the two groups were analyzed using the *t*-test or rank-sum test according to whether the data conformed to a normal distribution. The differences in plasma osteocalcin levels of and HOMA-IR between the two groups on different days were compared by Two Repeated Measures Factor ANOVA. Correlations between osteocalcin levels and BDNF levels were measured by linear correlation.

SPSS (SPSS Inc., Chicago, IL, USA) 22.0 was used for data analysis, and statistical significance was set at $P < 0.05$. Graphics were created using GraphPad Prism software (GraphPad Software, San Diego, CA, USA) 8.0 for Windows.

Results

Patient Demographics and Baseline Characteristics

A total of 318 adults were screened, and 212 older patients undergoing selective joint replacement were recruited and randomized into insulin (n = 106) and placebo (n = 106) groups. Ten patients in the insulin group and seven in the placebo group were excluded because they did not receive intervention with intranasal drugs, failed combined epidural anesthesia, or canceled surgery. Finally, 96 patients in the insulin group and 99 patients in the placebo group were analyzed in this study, including 145 female and 50 male patients (Figure 1).

Demographic data, comorbidities, surgery data, and biomarkers at baseline are shown in Table 1. The demographic data of the two groups were matched regarding sex, age, BMI, education, MMSE, physical activity, smoking, and alcohol habits. The medical history of the two groups was well-balanced, including self-reported cardiac disease, self-reported or imaging-diagnosed stroke/transient ischemic attack (TIA), self-reported hypertension, and self-reported diabetes. There

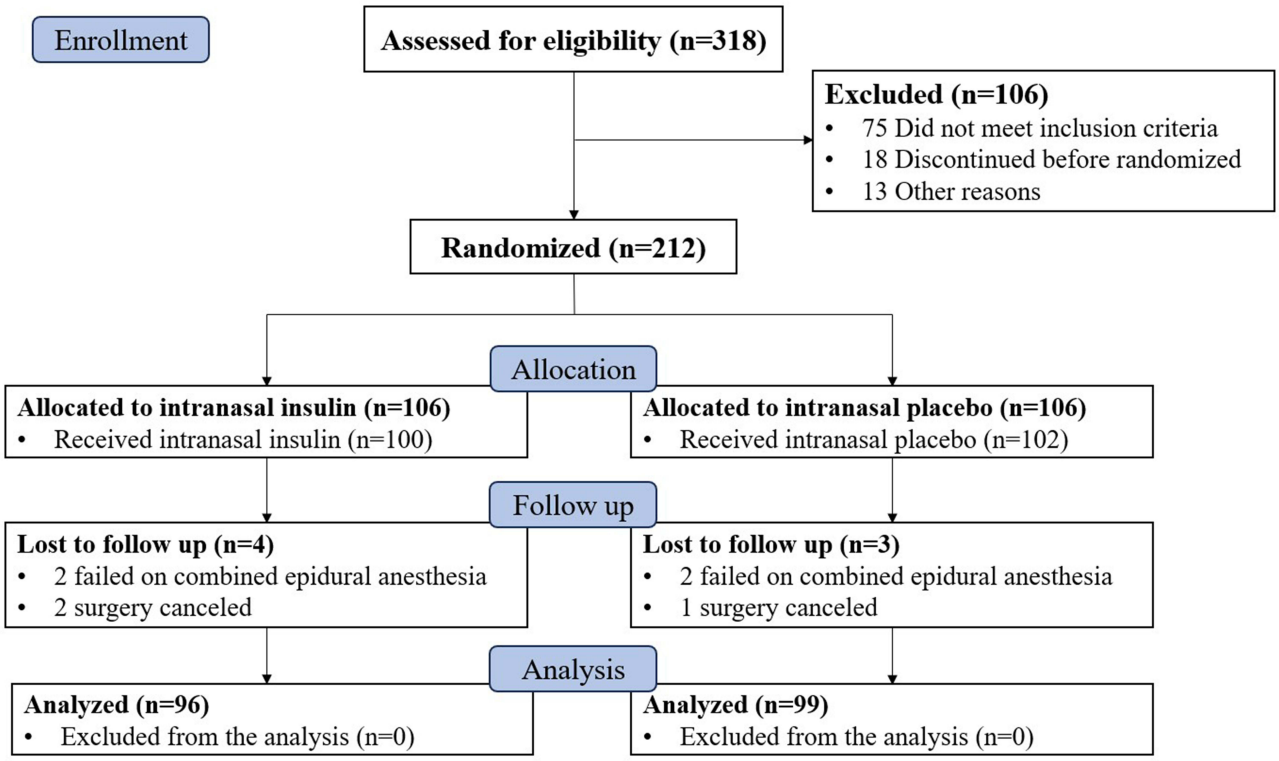

Figure 1 Flow Diagram.

were no significant differences in surgical types, preoperative fractures, duration of surgery, intraoperative blood loss, or visual analog scores between the insulin and placebo groups. Before the intervention, there were no significant differences in the levels of biomarkers in the plasma, including ucOC, tOC, insulin, glucose, and HOMA-IR.

Table 1 Baseline Demographic and Clinical Characteristics

Variable	Overall (n=195)	Insulin (n=96)	Placebo (n=99)
General data			
Age (y)	72.9±6.32	72.8±6.0	73.0±6.68
Female, n (%)	145 (74.35%)	72 (75%)	73 (76.04%)
BMI	23.46±3.44	23.06±3.09	23.84±3.72
Education (y)	7.7±4.58	7.4±4.58	7.9±4.60
MMSE	25.38±3.72	25.19±3.50	25.58±3.93
Physical activity			
Inactivity	89 (45.6%)	41 (42.7%)	48 (48.5%)
1–2 times/week	74 (37.9%)	37 (38.5%)	37 (37.4%)
>2 times/week	32 (16.4%)	18 (18.8.6%)	14 (14.1%)
Smoking, n (%)	20 (10.26%)	12 (12.5%)	8 (8.08%)
Alcohol, n (%)	8 (4.10%)	4 (4.17%)	4 (4.04%)
Self-reported cardiac disease, n (%)	33 (16.92%)	18 (18.75%)	15 (15.15%)
Self-reported or imaging diagnosed stroke/TIA, n (%)	30 (15.38%)	14 (14.58%)	16 (16.16%)
Self-reported hypertension, n (%)	98 (50.26%)	56 (58.33%)	42 (42.42%)
Self-reported diabetes, n (%)	46 (23.59%)	24 (25.26%)	22 (22.22%)
Insulin treatment, n (%)	18 (9.23%)	9 (9.47%)	9 (9.10%)
Oral hypoglycemic drugs, n (%)	28 (14.36%)	15 (15.79%)	13 (13.13%)

(*Continued*)

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Table 1 (Continued).

Variable	Overall (n=195)	Insulin (n=96)	Placebo (n=99)
Surgery data			
Surgical type/total hip, n (%)	103 (52.82%)	56 (58.33%)	47 (47.47%)
Preoperative fracture, n (%)	56 (28.72%)	32 (33.33%)	24 (24.24%)
Duration of surgery (hours)	4.08±1.30	4.01±1.23	4.15±1.43
Intraoperative blood loss (mL)	234.3±211.8	238.3±213.5	230.6±219.7
Visual Analogue Score	2.55±1.12	2.59±1.28	2.47±1.07
Baseline markers			
UcOC in plasma (ng/mL)	1.54±0.59	1.52±0.58	1.56±0.57
TOC in plasma (ng/mL)	13.36±8.48	13.25±8.78	13.47±8.92
UcOC/tOC in plasma (%)	15.94±12.27	16.05±10.36	15.89±11.53
Insulin in plasma (uU/mL)	34.09±10.15	34.87±10.32	33.64±9.52
Glucose in plasma (mmol/L)	5.26±0.91	5.31±0.98	5.19±0.76
HOMA-IR	7.99±2.79	8.21±2.95	7.75±2.40

Abbreviations: MMSE, mini-mental state examination; BMI, Body mass index; ucOC, uncarboxylated osteocalcin; tOC, total osteocalcin; HOMA-IR, Homeostasis assessment of insulin resistance.

Primary Outcome

Effects of Intranasal Insulin on the Incidence and Severity of POD

A total of 195 patients completed the trial, all of whom had completed the delirium assessment. Among the participants, 31 patients (15.90%) developed postoperative delirium, among which the incidence of POD in the insulin group (8/96, 8.33%) was significantly lower than the incidence in the placebo group (23/99, 23.3%) (Table 2; P=0.004). The incidence of POD was 29.0% (9/31), 51.6% (16/31), and 19.4% (6/31) for the hypoactive, hyperactive, and mixed types, respectively. The severity of delirium was mainly mild to moderate, with a median duration of 1.0 day in the insulin group and 2.0 days in the placebo group. The mean peak-DRS in the insulin group was significantly lower than that in the placebo group, as shown in Table 2 (P<0.001).

Secondary Outcome

Effect of Intranasal Insulin on Related Biomarkers

The levels of all biomarkers in the two groups after the intervention are presented in Supplementary Table 2. There were significantly differences in ucOC and tOC in cerebrospinal fluid and plasma between insulin and placebo groups on the day of surgery (D_0), the first day after surgery (D_1) and the third day after surgery (D_3). After 3 days of intranasal insulin intervention, ucOC, tOC, and BDNF levels in the cerebrospinal fluid were elevated in the insulin group on D_0, as shown in Figure 2 (P<0.001, P<0.001, P<0.001, respectively). A comparison of ucOC and tOC in plasma on different days between the two groups is shown in Figure 3. Plasma tOC levels were also significantly increased after the intervention in the insulin group on D_0, D_1, and D_3 (P<0.001, P<0.001, P<0.001, respectively). Plasma ucOC levels were significantly higher in the insulin group compared to the placebo group on D_0 (P<0.001) and significantly lower in the insulin group compared to the placebo group on

Table 2 Comparison of Postoperative Delirium Incidence and Severity Between Two Groups

Variable	Overall	Insulin Group	Placebo Group	*P* value
POD	31 (15.90%)	8 (8.33%)	23 (23.23%)	0.004*
Peak-DRS	8.01±6.0	6.01±3.5	9.94±7.1	<0.001*

Note: * P < 0.01.
Abbreviations: POD, postoperative delirium; Peak-DRS, peak values of the Delirium Rating Scale-98.

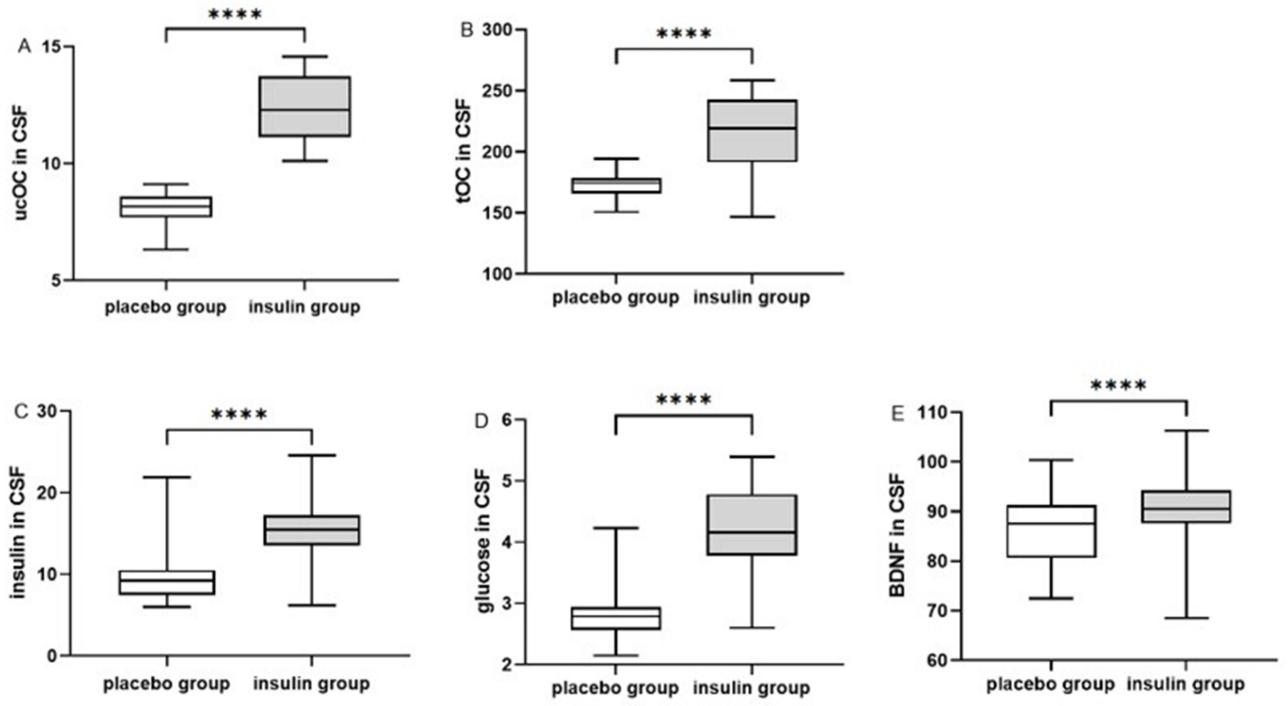

Figure 2 Comparison of biomarkers in cerebrospinal fluid between the two groups at the day of surgery. (**A**) The difference of ucOC levels in CSF between the two groups; (**B**) The difference of tOC levels in CSF between the two groups; (**C**) The difference of insulin levels in CSF between the two groups; (**D**) The difference of glucose levels in CSF between the two groups. (**E**) The difference of BDNF levels in CSF between the two groups. **** P<0.001.
Abbreviations: ucOC, uncarboxylated osteocalcin; tOC, total osteocalcin; BDNF, brain derived neurotrophic factor; CSF, cerebrospinal fluid.

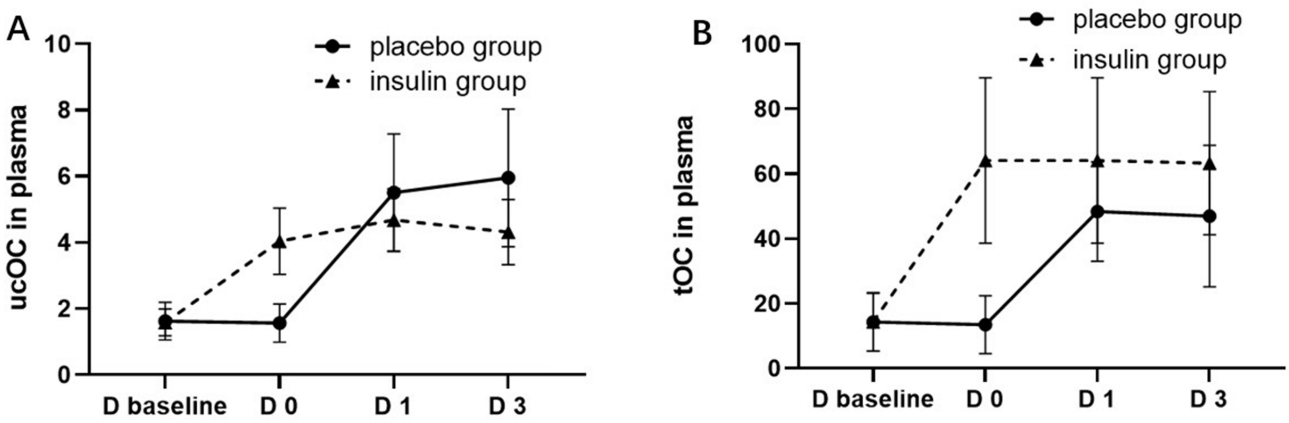

Figure 3 Changes of plasma osteocalcin levels in the two groups. (**A**) The line chart of ucOC level in two groups on $D_{baseline}$, D_0, D_1 and D_3. (**B**) Line chart of tOC level in two groups on $D_{baseline}$, D_0, D_1 and D_3. $D_{baseline}$, the day before intervention, D_0, the day of surgery, D_1, the first day after surgery, D_3, to the third day after surgery.
Abbreviations: ucOC, uncarboxylated osteocalcin; tOC, total osteocalcin.

D_1 and D_3 (P<0.001, P<0.001). To compare the difference in the percentage of ucOC to tOC between the two groups showed that the ratio of ucOC to tOC (ucOC/tOC) in insulin group was significantly lower than that in placebo group on D_0, D_1 and D_3 showed in Supplementary Table 3 (P<0.001, P<0.001, P<0.001).

Correlation Between Osteocalcin Levels and BDNF Levels

The correlation between osteocalcin and BDNF levels is shown in Supplementary Table 3. In all participants, ucOC levels were negatively associated with BDNF levels in the CSF (P=0.09). In the insulin group, ucOC and tOC levels were

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positively associated with BDNF levels in the CSF (P=0.01, P<0.01, respectively). However, there was no correlation between osteocalcin and BDNF levels in the placebo group.

Effect of Intranasal Insulin on Insulin, Glucose and HOMA-IR

Peripheral HOMA-IR in the insulin group was nearly the same as that in the placebo group at D_0 (P=0.669) and markedly decreased in the insulin group at D_3 (P=0.017) (Supplementary Figure 1).

In the plasma, there were no obvious differences in glucose levels between the two groups after the interventions on D_0, D_1, and D_3. The levels of insulin remained almost the same after the intervention on D_0, but visibly decreased in the insulin group compared to that in the placebo group on D_3. In the cerebrospinal fluid, insulin and glucose levels were elevated in the insulin group after 3 days of intranasal insulin intervention on D_0, as shown in Figure 2 (P<0.001, P<0.001).

Discussion

In this randomized, double-blind, placebo-controlled clinical trial, intranasal insulin significantly reduced the incidence and severity of postoperative delirium, improved peripheral insulin sensitivity and elevated osteocalcin levels in both cerebrospinal fluid and plasma in older patients undergoing joint replacement. It indicated that intranasal insulin could be a promising approach to prevent postoperative delirium in elderly patients, with osteocalcin potentially playing a key role in the mechanism through which intranasal insulin reduces postoperative delirium and enhances insulin sensitivity.

Intranasal insulin has been widely recognized for its significant improvement in short-term memory and cognitive function.[26] However, a long-term intervention study showed no obvious cognitive or functional benefits in patients with mild cognitive impairment or Alzheimer's disease.[27] Encouragingly, numerous animal and clinical studies have shown that intranasal insulin holds promising potential for addressing transient and reversible perioperative neurocognitive impairment.[9,10,28,29] Our findings further support the effectiveness of intranasal insulin in the prevention and treatment of postoperative delirium, while also exploring its possible underlying mechanisms.

The mechanisms through which intranasal insulin improves postoperative delirium are complex and multifaceted. Delirium is accompanied by regional cerebral hypometabolism, as observed on 18F-FDG PET/CT scan.[30] Impaired glucose utilization and a shift to ketone body metabolism occurred in the brain in older patients experiencing delirium after hip fracture.[31] Insulin resistance, another indicator of glucose metabolism disorders, has also been shown to correlate with postoperative delirium.[25,32] Our findings showed that the mean central glucose concentration in the insulin group (4.57 mmol/L) was significantly higher than that in the placebo group (2.83 mmol/L), following intranasal insulin administration. Intranasal insulin has been shown to increase central brain energy levels in healthy subjects.[33] Under PET imaging, intranasal insulin can increase glucose levels and restore glucose metabolism in multiple regions of the brain, thereby improving cognitive function.[34] Furthermore, intranasal insulin notably increased the central insulin levels in our study, which may contribute to reducing brain insulin resistance. Brain insulin resistance, a pathological feature of metabolic and cognitive diseases, is characterized by decreased insulin uptake and sensitivity, possibly due to insulin resistance at the blood-brain barrier.[35,36] By directly increasing central insulin levels and addressing brain insulin resistance, intranasal insulin can improve cognitive function. These findings align with established mechanisms of intranasal insulin, supporting its role in enhancing central energy metabolism and cognitive function.

Notably, intranasal insulin rapidly increased the central and peripheral osteocalcin levels in our study, which may be a novelty mechanism of intranasal insulin in improving cognition. Osteocalcin, a bone-derived hormone, is necessary to promote normal brain development and function and has recently been shown to be capable of reversing the cognitive manifestations of aging.[37] Osteocalcin knockout mice showed significantly increased anxiety-like behavior and severe deficits in learning and memory, which could be fully corrected by central supplementation with osteocalcin.[15] The increase in serum osteocalcin was correlated with an improvement in cognitive dysfunction after liraglutide therapy in diabetic rats, supporting the protective effect of elevated peripheral osteocalcin on cognition.[38] After middle age, circulating osteocalcin levels decline, contributing in part to age-related cognitive decline. In aged mice, central osteocalcin supplementation is necessary and sufficient to correct age-related cognitive decline, with strong animal evidences indicating that elevated central osteocalcin improves cognition.[19] Our results provide indirect clinical evidence that elevated central and peripheral osteocalcin levels can improve cognition. The underlying mechanism may be related

to the elevation of central brain-derived neurotrophic factor (BDNF) levels. In our study, BDNF levels in the CSF were notably increased after intranasal insulin intervention, and there was an apparent correlation between osteocalcin and BDNF levels in the CSF of the insulin group, but not in the placebo group. This indicates that the elevation of BDNF levels is associated with osteocalcin levels during intranasal insulin administration. BDNF, a member of the neurotrophin protein family, plays a crucial role in cognitive function for the regulation of the development, maintenance, and plasticity of the nervous system. Therefore, the elevation of osteocalcin and BDNF levels might be associated with the mechanism by which intranasal insulin improves cognitive function.

Unlike total osteocalcin, the effect of peripheral uncarboxylated osteocalcin on cognitive function is controversial. Some studies suggest that higher serum uncarboxylated osteocalcin levels may protect cognition, showing a positive correlation with cognitive impairment in rats and males with type 2 diabetes.[39,40] On the contrary, other research indicated that elevated plasma uncarboxylated osteocalcin levels are associated with impaired cognitive function in community-dwelling older adults.[41] In our previous study, preoperative uncarboxylated osteocalcin level in cerebrospinal fluid was an independent risk factor for postoperative delirium in older patients undergoing joint replacement.[25] In this study, the level of uncarboxylated osteocalcin in the insulin group was significantly lower than that in the placebo group after surgery, although intranasal insulin elevated the uncarboxylated osteocalcin levels before surgery. Additionally, intranasal insulin significantly reduced the ratio of uncarboxylated osteocalcin to total osteocalcin. It seems that elevated levels of uncarboxylated osteocalcin and its ratio to total osteocalcin are risk factors for cognitive function in our study.

Besides, osteocalcin may also be associated with the mechanism by which intranasal insulin improves peripheral insulin sensitivity. In our study, intranasal insulin promptly increased the plasma total osteocalcin level and subsequently improved peripheral HOMA-IR. A bidirectional positive feedback mechanism exists between osteocalcin and insulin.[20] Insulin signaling in osteoblasts can promote the secretion of osteocalcin, which in turn can promote the secretion of insulin and improve insulin sensitivity. Hence, improving insulin signaling in osteoblasts might help to increase circulating osteocalcin levels and further improve insulin sensitivity by promoting insulin secretion and glucose uptake in tissues. Evidence supports that plasma osteocalcin is positively related to insulin sensitivity[42] and increased plasma osteocalcin levels are linked to the improvement of insulin sensitivity.[14] This suggested that osteocalcin may be involved in the molecular mechanism by which intranasal insulin improves peripheral HOMA-IR and insulin sensitivity. Although further research is needed to confirm the potential role of osteocalcin in the mechanism of intranasal insulin, it appears to be a promising molecule that could help explain the effect of intranasal insulin on both peripheral metabolism and cognitive function.

Conclusions

In conclusion, our study found that intranasal insulin significantly reduced the incidence and severity of postoperative delirium, and improved central and peripheral osteocalcin levels and insulin sensitivity in older patients undergoing joint replacement. This study not only broadens the potential use of intranasal insulin in the prevention of postoperative delirium but also suggested the potential role of osteocalcin in the mechanism through which intranasal insulin rescues peripheral metabolism and cognitive function.

Strengths and Limitations

In our study, we conducted delirium assessments twice a day in the morning and at the first half of the night, which also means that delirium occurring at the second half of the night may not have been detected. The rate of the undiscovered POD in the primary outcome was very low; therefore, we consider the results of this study credible in assessing postoperative delirium. Further research is needed to show the duration of intranasal insulin on elevating osteocalcin.

Copyright Statement

Data Sharing Statement

The data for this manuscript will be made available by the authors to qualified researchers upon reasonable request. Requests to access the data should be directed to the corresponding author.

Ethics Statement

This study was approved by the Ethical Committee of the Third Xiangya Hospital of Central South University (IRB K22051), and written informed consent was obtained from all participants. The study complied with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work. This paper has been partly uploaded to Medrxiv as a preprint: https://www.medrxiv.org/content/10.1101/2024.07.02.24309290v1.

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