Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Risk Factors of Delirium Following Reconstructive Surgery for Head and Neck Tumors: A Retrospective Clinical Trial

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Background: Patients after head and neck tumor reconstruction surgery frequently require deep sedation and analgesia in the ICU. However, the risk factors for delirium associated with propofol-based sedation remain unclear.

Objective: The study aimed to explore the risk factors of delirium of propofol singled or combined sedation.

Methods: This retrospective study analyzed ICU patients who underwent head and neck tumor reconstruction surgery. The patients were divided into three groups: propofol (P), propofol + midazolam (PM), and propofol + dexmedetomidine (PD) groups. We utilized univariate and multivariate logistic regression to identify risk factors of delirium.

Results: Delirium occurred in 4 (7.02%), 11 (28.21%), and 5 (20.83%) patients in the P, PM and PD groups, respectively. Elevated mean arterial pressure (MAP), increased aspartate aminotransferase (AST) levels, and the combined use of midazolam were determined to be significant risk factors for delirium in this patient cohort. The combined use of midazolam is the strongest predictor of delirium, which can increase the risk of delirium by 3.218 times (95% CI = 1.041–9.950, p = 0.042).

Conclusion: Propofol combined with midazolam for sedation in patients after head and neck tumor reconstruction surgery may increase the risk of delirium.

Keywords: head and neck tumor reconstruction, delirium, propofol, midazolam, sedation, ICU

Background

Patients undergoing head and neck tumor reconstruction surgery often experience postoperative swelling, potentially obstructing the respiratory tract. The routine surgical procedures for head and neck tumor reconstruction typically involve the resection of pathological tissues, lymph node dissection, flap preparation, flap transfer for repair, reconstruction, and most patients also undergo temporary tracheostomy.[1,2] To prevent mechanical damage to the transplanted and reconstructed tissues from spontaneous movement, deep sedation (Richmond Agitation and Sedation Scale (RASS) ≤−4 points or Ramsay scales ≥5 points) is often required for a certain period postoperatively.[3] Deep sedation may cause hypotension, potentially reducing flap perfusion and increasing the risk of perfusion insufficiency and flap necrosis. Consequently, close postoperative monitoring in the ICU is necessary.[4] Despite this, a study has shown that ICU admission after head and neck surgery does not necessarily reduce the incidence of complications.[5] The decision to transfer patients to the ICU is evaluated and determined by the head and neck surgeons. To et al suggested that it is more safe to extubate within 24 to 48 hours after surgery for patients without tracheotomy.[6] Postoperative sedation goals in major head and neck reconstruction surgery include rapid achievement of full sedation, rapid recovery following drug reduction or cessation, and prompt weaning from the ventilator or extubation.

Received: 28 May 2024
Accepted: 14 January 2025
Published: 24 January 2025

Delirium is a common and serious complication in patients admitted to the ICU after major surgery.[7,8] The incidence of delirium in patients undergoing major head and neck surgery ranged from 11.50% to 36.11%.[8] The neuropathophysiology of delirium includes neurotransmitter hypotheses, neuroendocrine hypotheses, circadian rhythm dysregulation or melatonin dysregulation hypotheses, and network disconnectivity hypotheses.[9] Delirium is associated with multifactorial causes, such as age, gender, length of operation, hypertension, diabetes, blood transfusion, tracheotomy, insufficient analgesia, and fever.[7,8,10,11]

At present, the sedative drugs used in clinic mainly include propofol, midazolam and dexmedetomidine. Propofol acts on the γ-aminobutyric acid subtype A (GABAa) receptor, providing rapid sedation and awakening.[12] Midazolam is a traditional benzodiazepine with anti-anxiety effects and high anterograde amnesia rates during sedation.[13] Dexmedetomidine, a highly selective central agent α-2 adrenergic receptor agonists,[14] increases the safety and comfort of long-term sedation in critically ill patients.[15]

Studies have indicated that sedative drugs, such as midazolam and propofol, might be independent risk factors for delirium.[11,16] A combined sedation strategy is often used to achieve targeted sedation in patients requiring deep sedation and analgesia in the ICU;[17] however, research on its efficacy in reducing delirium compared to propofol-single sedation is limited.

This study aims to explore the risk factors of delirium associated with propofol single or combined sedation in patients undergoing head and neck tumor reconstruction surgery, focusing on the incidence of delirium, sedation success rate, weaning/extubation time, duration of mechanical ventilation, length of stay (LOS) in ICU and hospital, and safety events.

Materials and Methods

Study Design

We conducted a retrospective cohort study on a comprehensive ICU with 79 beds at Nanfang Hospital of Southern Medical University. This study was granted exemption from informed consent by the Ethics Committee due to its retrospective nature and was approved under the protocol number NFEC-2023-077. The study complied with the declaration of Helsinki, and all patients' data were anonymized to ensure privacy.

Study Population

Patients who underwent head and neck tumor reconstruction surgery and were admitted to the ICU from September 2017 to February 2022 were included. Inclusion criteria were age ≥18 years, requirement for mechanical ventilation, and immediate need for sedation and analgesia. Exclusion criteria included repeat ICU admissions, admission for reasons other than head and neck tumor reconstruction, inability to obtain monitoring data, lack of sedation and analgesia post-ICU admission, and patients with a history of delirium, confusion/disorientation, and other neurological disorders, as well as a history of psychiatric disorders, severe liver or kidney dysfunction (Child-Pugh grade 3 or uremic stage renal function).

Data Collection

Demographic data, vital signs at specific sedation intervals (H0, H4, H12, H24 after ICU admission), and baseline blood results were collected. Additionally, liver and kidney function, blood gas analysis, vasopressor use, acute physiology and chronic health evaluation II (APACHE II), sedative and analgesic drug types and doses, Ramsay scores, and sedation success rates were recorded. Duration of sedation, weaning/extubation time, duration of mechanical ventilation, LOS ICU and hospital were calculated and recorded. Complications such as hypotension, bradycardia, hypertension, fever, delirium (diagnosed using Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)) and central nervous system complications such as cerebral infarction, cerebral hemorrhage, as well as cardiac arrest were also documented. The start and end time of anesthesia and surgery and time from anesthetic induction and weaning/extubation were also collected and calculated by an anesthesiologist.

Patient Management

All patients were fully conscious and without neurological or psychiatric behavioral abnormalities before surgery. They all underwent total anesthesia surgery with target-controlled infusion (TCI) of combined intravenous and inhalation anesthesia.

Postoperative care for patients admitted to the ICU after head and neck tumor reconstruction surgery was determined by the ICU chief physician and relative surgeons. Management included daily dressing changes in the surgical area, monitoring of microvascular blood flow, and administration of antibiotics and dexamethasone as needed. Fluid therapy was adjusted to maintain blood volume, and red blood cells or human blood albumin was administered for anemia and hypoalbuminemia, respectively. Vasopressors were used to maintain blood pressure above 120/90mmHg. Sedation depth was determined by the ICU physician, with nurses assessing sedation and analgesia daily using the Critical Care Pain Observation Tool (CPOT) and Ramsay scales, adjusting drug dosages accordingly.

Study Endpoints

The primary endpoint was the incidence of delirium and its risk factors. Secondary endpoints included sedation success rate, weaning/extubation time, duration of mechanical ventilation, ICU and hospital length of stay, and safety events related to hypotension, bradycardia, hypertension, fever, cerebral infarction, and cerebral hemorrhage, as well as cardiac arrest.

Statistical Analysis

SPSS 22.0 was used for data processing. Bilateral test ($p < 0.05$) was considered to have significant difference.

Continuous variables conforming to the normal distribution are expressed as mean ± SD, while those not conforming to the normal distribution are expressed as medium (IQR25-IQR75), and classified variables are expressed as n (%).

The difference of continuous variables among the three groups was compared using one-way ANOVA for those conforming to normal distribution, non-parametric test (Kruskal–Wallis test) for those not conforming to normal distribution, and chi-square test or Fisher's exact test for categorical variables. LSD or DUNNETT t3 test was used for comparison between the three groups. Univariate and multivariate binary logistic regression analyses were used to analyze risk factors of delirium, and OR value, 95% confidence interval (CI) and p value were obtained.

Results

Study Population

From September 2017 to February 2022, 137 patients who underwent head and neck tumor reconstruction surgery were admitted to the ICU. Based on the inclusion and exclusion criteria, 120 patients were included in the study. All patients received propofol sedation: 57 in the propofol group (P), 39 in the propofol + midazolam group (PM), and 24 in the propofol + dexmedetomidine group (PD). No patients received midazolam or dexmedetomidine alone or in combination with both (Figure 1).

There were no significant differences among the groups in terms of demographic data, vital signs, and baseline blood results like liver and kidney function, blood gas analysis (except for partial pressure of carbon dioxide (pCO_2)), or prevalence of comorbidities such as hypertension, diabetes, prior malignancy, and personal habits including smoking, drinking, and betel nut chewing. APACHE II scores and vasopressor use within 24 hours were also similar among the three groups. Duration of surgery and anesthesia also showed no significant difference among the three groups. However, the P group had a significantly shorter time from anesthetic induction to weaning/extubation compared to the PM group ($p = 0.045$). The PD group had a higher pCO_2 ($p = 0.017$) and a greater proportion of dopamine use ($p = 0.000$) compared to the P and PM groups (Table 1).

Incidence of Delirium Among the P, PM and PD Groups

According to CAM-ICU assessment, the overall incidence of delirium among patients after head and neck tumor reconstruction surgery was 16.67%. Delirium occurred in 4 (7.02%), 11 (28.21%), and 5 (20.83%) patients in the P,

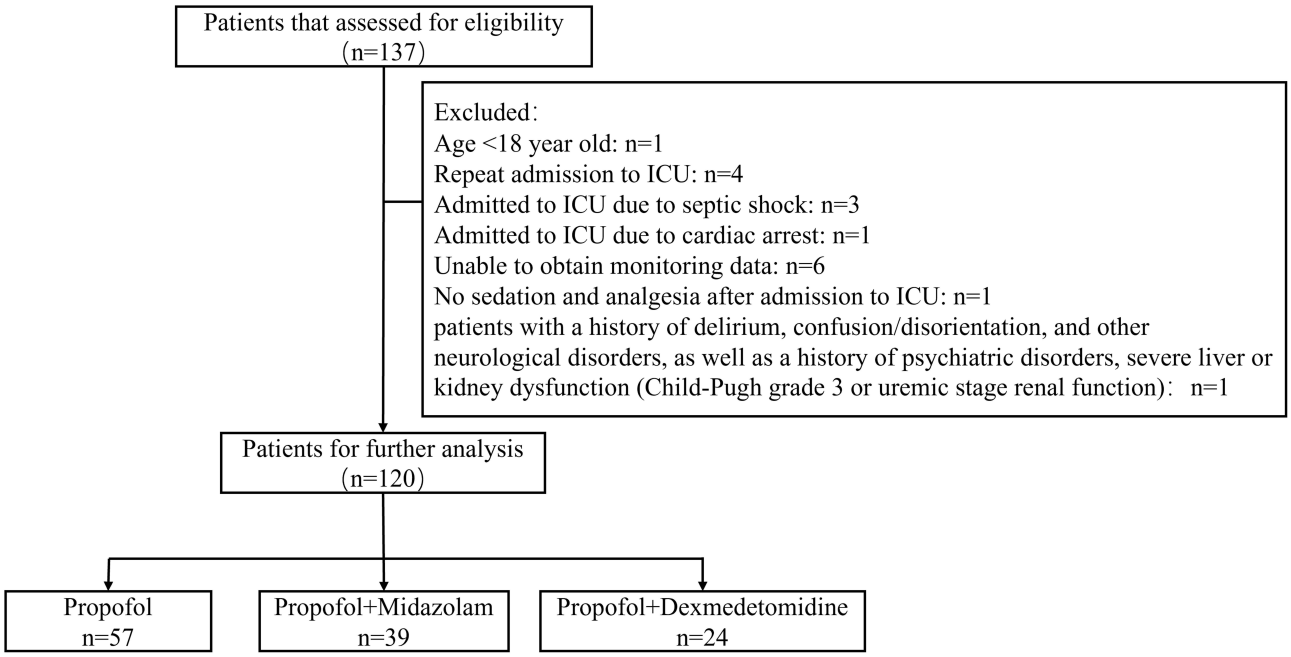

Figure 1 Flow chart of patients.

PM and PD groups, respectively, with a significant difference observed among the three groups (p = 0.016) (Figure 2). Univariate logistic regression analysis revealed a significant difference in delirium rates among the groups (OR = 1.025, 95% CI = 1.04–1.046, p = 0.018). Pairwise comparisons indicated that the P group had a significantly lower delirium rate compared to the PM group (p = 0.009), while no significant differences were found between the P and PD groups or the PM and PD groups (Figure 3A, STable 1).

Table 1 Clinical and Demographic Characteristics of Patients in P, PM and PD Groups

	Total n=120	**P n=57**	**PM n=39**	**PD n=24**	**p**
Age, y, mean (SD)	56.16 (12.18)	56.25 (13.34)	55.82 (11.09)	56.50 (11.46)	0.975
BMI, kg/m^2, mean (SD)	22.58 (3.19)	22.22 (3.38)	22.89 (3.12)	22.96 (2.85)	0.496
Sex-male, n(%)	83 (69.20)	37 (64.90)	30 (76.90)	16 (66.67)	0.437
HR, bpm, mean (SD)	86.32 (19.78)	82.86 (19.56)	86.54 (19.04)	94.17 (19.99)	0.062
RR, /min, median (IQR)	12.00 (12.00,15.00)	12.00 (12.00,14.00)	13.00 (12.00,15.00)	12.00 (12.00,15.00)	0.268
SBP, mmHg, mean (SD)	147.43 (102.11)	136.51 (27.68)	137.90 (26.25)	188.88 (22.68)	0.083
DBP, mmHg, mean (SD)	77.48 (14.77)	76.30 (15.12)	76.13 (12.14)	82.50 (17.20)	0.178
MAP, mmHg, mean (SD)	97.21 (17.86)	95.47 (17.85)	96.46 (15.90)	102.54 (20.45)	0.255
SpO_2, %, median (IQR)	100.00 (100.00,100.00)	100.00 (100.00,100.00)	100.00 (100.00,100.00)	100.00 (100.00,100.00)	0.188
WBCs, ×10^9/L, mean (SD)	11.38 (3.72)	11.23 (3.52)	11.12 (4.08)	12.18 (3.60)	0.505
Hgb, g/L, mean (SD)	116.47 (18.68)	115.67 (17.25)	114.23 (19.59)	122.00 (20.11)	0.252
NEU%, mean (SD)	84.02 (7.57)	84.65 (7.86)	83.60 (7.22)	83.25 (7.62)	0.690
PLT, ×10^9/L, median (IQR)	197.00 (166.00,249.00)	194.00 (159.50,260.50)	196.00 (162.00,250.00)	202.50 (177.50,238.50)	0.663
ALB, g/L, median (IQR)	32.60 (29.80,36.10)	32.50 (29.93,35.00)	32.80 (29.20,36.30)	32.75 (28.93,38.70)	0.657
ALT, U/L, median (IQR)	13.00 (9.00,20.00)	13.00 (9.00,18.00)	15.00 (9.00,23.00)	12.00 (9.00,22.00)	0.825
AST, U/L, median (IQR)	20.00 (17.00,26.00)	21.00 (17.00,24.50)	20.00 (16.00,31.00)	21.00 (17.00,26.00)	0.857
BUN, mmol/L, mean (SD)	3.79 (1.14)	3.83 (1.12)	3.82 (1.15)	3.62 (1.18)	0.722

(*Continued*)

Table 1 (Continued).

	Total n=120	P n=57	PM n=39	PD n=24	p
CR, umol/L, mean (SD)	68.02 (18.28)	67.00 (17.71)	69.18 (19.09)	68.54 (18.93)	0.840
pH, mean (SD)	7.37 (0.06)	7.38 (0.05)	7.36 (0.05)	7.36 (0.08)	0.311
pO_2, mmHg, mean (SD)	167.25 (37.68)	169.75 (36.56)	158.76 (37.22)	176.41 (41.45)	0.299
pCO_2, mmHg, mean (SD)	40.23 (6.70)	38.31 (5.17)	41.77 (6.62)	43.22 (9.30)	0.017
Lac, mmol/L, median (IQR)	1.10 (0.80,1.95)	1.10 (0.80,1.60)	1.20 (0.73,2.00)	1.50 (0.85,2.13)	0.636
PaO_2/FiO_2, mmHg, mean (SD)	418.51 (100.11)	430.34 (99.83)	391.29 (103.35)	435.79 (89.38)	0.214
Underlying diseases, n (%)					
Hypertension	11 (9.20)	4 (7.00)	4 (10.30)	3 (12.50)	0.707
Diabetes	10 (8.30)	4 (7.00)	4 (10.30)	2 (8.30)	0.853
Malignant tumor (excluding oral and maxillofacial)	5 (4.20)	2 (3.50)	1 (2.60)	2 (8.30)	0.508
Personal history, n (%)					
Smoking	60 (50.00)	26 (45.60)	23 (59.00)	11 (45.80)	0.394
Drinking	44 (36.70)	20 (35.10)	19 (48.70)	5 (20.80)	0.078
Chewing betel nut	9 (7.50)	5 (8.80)	1 (2.60)	3 (12.50)	0.306
APACHE II, mean (SD)	9.91 (4.38)	9.21 (4.36)	10.69 (4.53)	10.29 (4.05)	0.238
Duration of surgery, mean (SD)	6.93 (2.25)	6.75 (1.92)	6.84 (2.53)	7.49 (2.47)	0.386
Duration of anesthesia, mean (SD)	8.39 (2.26)	8.13 (1.90)	8.44 (2.62)	8.92 (2.45)	0.354
Time from anesthetic induction and weaning/extubation, median (IQR)	55.30 (31.49, 75.10)	45.18 (27.75, 74.4)	71.75 (50.40, 75.13)	62.28 (45.76, 76.40)	0.045
Combined medication, n (%)					
Isoproterenol	14 (11.70)	4 (7.00)	4 (10.30)	6 (25.00)	0.095
Norepinephrine	16 (13.30)	12 (21.10)	2 (5.10)	2 (8.30)	0.070
Dopamine	33 (27.50)	1 (1.80)	16 (41.00)	16 (66.70)	0.000

Abbreviations: P, Propofol; PM, Propofol+ Midazolam; PD, Propofol+ Dexmedetomidine; SD, Standard Deviation; BMI, Body Mass Index; HR, Heart rate; RR, Respiratory rate; IQR, Interquartile Range; SBP, Systolic pressure; DBP, Diastolic pressure; MAP, Mean arterial pressure; SpO_2, Peripheral capillary oxygen saturation; WBCs, White blood cell counts; Hgb, Hemoglobin; NEU%, Percentage of neutrophils; PLT, Platelet; ALB, Albumin; ALT, Alanine transaminase; AST, Aspartate transaminase; BUN, Urea nitrogen; CR, Creatinine; pO_2, Partial pressure of oxygen; pCO_2, Partial pressure of carbon dioxide; Lac, Lactate; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Secondary Endpoints Among the P, PM and PD Groups

Significant differences were observed in the sedation success rate ($p = 0.021$), duration of mechanical ventilation ($p = 0.019$), and LOS ICU ($p = 0.001$) among the three groups. The PM group exhibited the highest sedation success rate, the longest duration of mechanical ventilation, and the longest LOS ICU. Pairwise comparisons revealed that the PM group had a higher sedation success rate than the PD group ($p = 0.016$). Compared to the P group, the PM group had a significantly longer LOS ICU ($p = 0.000$), while the duration of mechanical ventilation did not differ significantly. There were no significant differences in weaning/extubation time ($p = 0.581$) or LOS hospital ($p = 0.078$) among the three groups (Figure 3B–F, STable 1).

Safety Events Among the P, PM and PD Groups

No significant differences were found among P, PM and PD groups in safety events including hypotension ($p = 0.224$), bradycardia ($p = 0.799$), hypertension ($p = 0.760$), and postoperative fever ($p = 0.372$). None of the patients experienced cerebral infarction or cerebral hemorrhage, which could lead to persistent neurological complications. Only one patient experienced cardiac arrest due to asphyxiation following massive hemorrhage in the surgical field in the P group, and the patient failed to be rescued and died (Figure 4, STable 1).

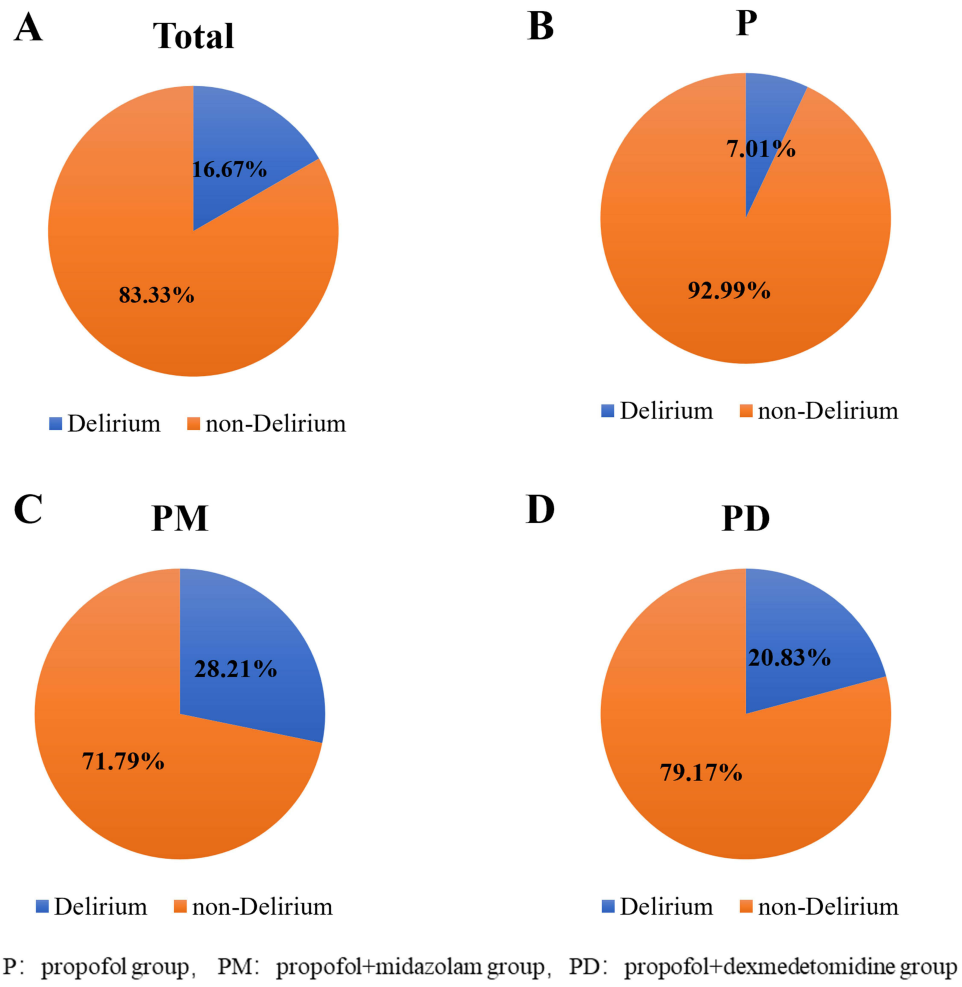

Figure 2 Incidence of delirium among the P, PM and PD group. (**A**) Total population, (**B**) P group, (**C**) PM group, and (**D**) PD group.

Doses of Sedative and Analgesic Drugs Among the P, PM and PD Groups

For sedative drug doses, the median daily doses of propofol in the P, PM and PD groups were 1.80 g, 1.40 g, and 1.60 g, respectively. The median daily dose of midazolam in the PM group was 38.00 mg, and for dexmedetomidine in the PD group, it was 137.10 μg. No significant difference in propofol doses was found among the three groups (p = 0.336) (Table 2).

Regarding analgesic doses, due to the independent selection by physicians, patients received various analgesics including remifentanil, butorphanol tartrate, hydromorphone hydrochloride, fentanyl, and sufentanil (data not shown). Focusing on the impact of sedative drugs, we converted all analgesic doses to morphine equivalents for analysis, and using established conversion ratios,[18] it is proposed to convert the dose of each analgesic drug into morphine equivalent for statistical analysis. The specific conversion formula is as follows: 1 mg remifentanil = 100 × 1mg morphine, 1mg butorphanol tartrate = 7 × 1mg morphine, 1mg hydromorphone hydrochloride = 4 × 1mg morphine, 1mg fentanyl = 100 × 1 mg morphine, 1 mg sufentanil = 1 × 1 mg morphine. The median morphine equivalent daily doses for the P, PM, and PD groups were 98.00 mg, 100.00 mg, and 103.80 mg, respectively, with no significant difference among the groups (p = 0.359) (Table 2).

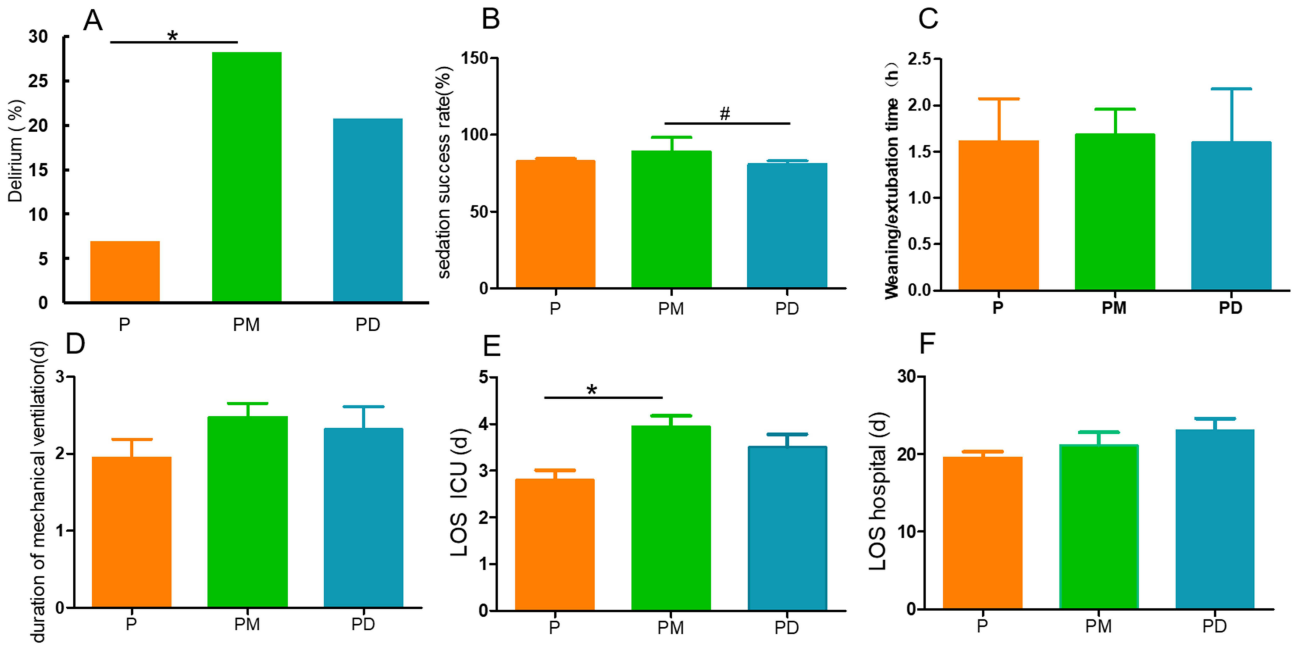

Figure 3 Comparisons of primary and secondary endpoints of the patients in P, PM and PD group. (**A**) Delirium (%) *p=0.009, (**B**) Sedation success rate (%), #p=0.016, (**C**) Weaning/extubation time (h), (**D**) Duration of mechanical ventilation (d), (**E**) Length of stay in ICU (d), *p=0.000, (**F**) Length of stay in hospital (d). *p<0.05/3=0.017 was recognized as significant.

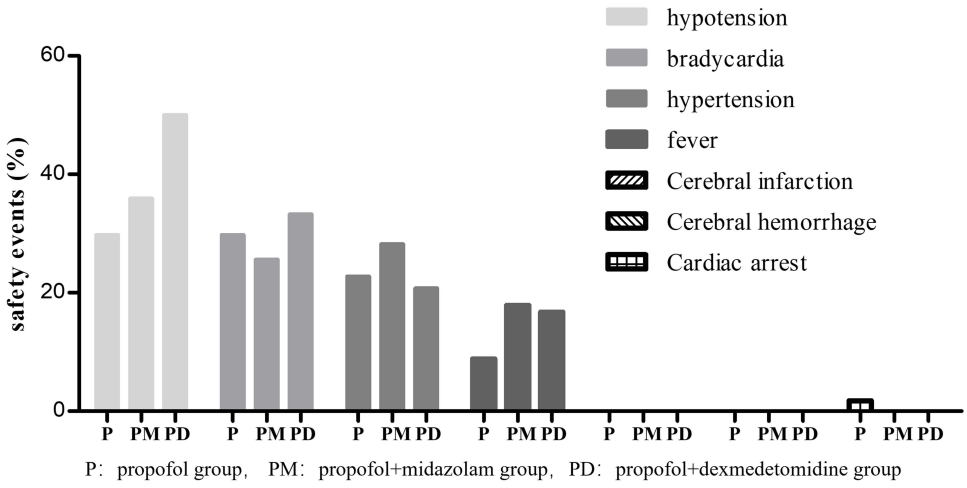

Figure 4 Safety events of the patients in the P, PM and PD group.

Risk Factors for Delirium in Patients After Head and Neck Tumor Reconstruction Surgery

To identify delirium risk factors in mechanically ventilated patients after head and neck tumor reconstruction admitted to the ICU, we conducted univariate logistic regression analysis with baseline variables. The analysis identified several factors associated with delirium, including male sex, diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), weaning/extubation time, dopamine use, and sedation with either propofol alone or in combination with midazolam (all p <0.05) (Table 3).

https://doi.org/10.2147/TCRM.S480272

Table 2 Doses of Sedative and Analgesia Drugs of the Patients in P, PM and PD Group

	P	PM	PD	p
Propofol (g/d), median (IQR)	1.80 (1.20, 2.40)	1.40 (1.20, 2.00)	1.60 (1.20, 2.40)	0.336
Midazolam (mg/d), median (IQR)	–	38.00 (25.00, 62.50)	–	–
Dexmedetomidine (ug/d), median (IQR)	–	–	137.10 (88.10, 287.50)	–
Morphine equivalent (mg/d), median (IQR)	98.00 (64.80, 124.50)	100.00 (71.70, 145.50)	103.80 (71.50, 139.00)	0.359

Abbreviations: P, Propofol; PM, Propofol+ Midazolam; PD, Propofol+ Dexmedetomidine; IQR, Interquartile Range.

Table 3 Factors Associated with Delirium in Univariate Logistic Regression

	Delirium n=20	Non-delirium n=100	OR, 95% CI	p
Sex-male, n (%)	18 (90.00)	65 (65.00)	4.846 (1.062, 22.104)	0.042
DBP, mmHg, mean (SD)	84.70 (15.01)	76.04 (14.37)	1.041 (1.006, 1.076)	0.020
MAP, mmHg, mean (SD)	107.65 (18.41)	95.12 (17.08)	1.040 (1.011, 1.070)	0.007
RR, /min, median (IQR)	14.00 (12.00, 17.25)	12.00 (12.00, 14.00)	1.189 (1.014, 1.393)	0.033
ALT, U/L, median (IQR)	17.00 (11.25, 32.75)	12.00 (9.00, 18.75)	1.046 (1.010, 1.083)	0.011
AST, U/L, median (IQR)	25.50 (20.25, 34.75)	20.00 (17.00, 24.00)	1.066 (1.018, 1.116)	0.007
Weaning/extubation time, h, median (IQR)	0.02 (0.00, 0.04)	0.05 (0.01, 0.12)	0.030 (0.002, 0.600)	0.022
Dopamine, n (%)	10 (50.00)	23 (23.00)	3.348 (1.241, 9.033)	0.017
Single sedation of propofol, n (%)	4 (20.00)	53 (53.00)	0.222 (0.069, 0.710)	0.011
Combined sedation with midazolam, n (%)	11 (55.00)	28 (28.00)	3.143 (1.176, 8.400)	0.022

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval; DBP, Diastolic pressure; SD, Standard Deviation; MAP, Mean arterial pressure; RR, Respiratory rate; IQR, Interquartile Range; ALT, Alanine transaminase; AST, Aspartate transaminase.

Table 4 Factors Associated with Delirium in Multivariable Logistic Regression

	p	aOR	95% CI
MAP	0.009	1.043	1.010, 1.077
AST	0.016	1.064	1.011, 1.119
Combined sedation with midazolam	0.042	3.218	1.041, 9.950

Abbreviations: aOR, Adjusted odds ratio; 95% CI, 95% Confidence interval; MAP, Mean arterial pressure; AST, Aspartate transaminase.

In multivariate binomial logistic regression, including male sex, DBP, MAP, RR, ALT, AST, dopamine use, and sedation regimens, elevated MAP, AST, and midazolam combination sedation were identified as risk factors for delirium. Notably, midazolam combination sedation was the strongest predictor, increasing delirium risk by 3.218 times (95% CI = 1.041, 9.950, p = 0.042) (Table 4).

Discussion

This study retrospectively evaluated the risk factors associated with propofol sedation, either alone or in combination with midazolam or dexmedetomidine, in patients admitted to the ICU following head and neck tumor reconstruction surgery. The incidence of delirium was 16.67%, with the PM group showing the highest rate at 28.21%, significantly higher than the P group at 7.02% and the PD group at 20.83%. Elevated MAP, increased AST level, and midazolam combination sedation were identified as significant risk factors for delirium during ICU stay.

These findings underscore the importance of sedation strategy in the development of delirium after ICU admission. The higher incidence of delirium in the PM group suggests that the combined use of midazolam with propofol may increase the risk of delirium, a condition associated with adverse outcomes including increased hospitalization costs,

prolonged LOS, increased mortality, and long-term cognitive impairment.[19] This highlights the need for careful consideration in the selection of sedative drugs, especially in patients with high sedation and analgesia requirements.[20] The selection of sedative drugs and the use of sedation scales, such as the RASS and Ramsay score,[21] to guide sedation practices and avoid oversedation may help prevent delirium.[20]

The present study aligns with previous research indicating that midazolam sedation is a risk factor for delirium in critically ill patients. A large prospective randomized controlled study confirmed higher delirium rates among mechanically ventilated ICU patients sedated with midazolam compared to dexmedetomidine (54.0% vs 76.7%, $p < 0.001$).[22] Subsequent studies have also identified midazolam sedation as a risk factor for delirium in critically ill patients.[23–25] Notably, all patients received sedation with propofol, and doses of propofol were reduced by using midazolam or dexmedetomidine. Univariate logistic regression analysis suggested that propofol alone was a protective factor against delirium, while midazolam combination increased the incidence of delirium, aligning with literature on midazolam's risk.[22,23,26] A recent randomized controlled study found that sequential midazolam and dexmedetomidine use could achieve target sedation levels, shorten extubation time, promote recovery, and reduce delirium incidence,[27] suggesting that dexmedetomidine could be a preferable alternative to midazolam in sedation protocols, particularly in patients at high risk for delirium.

Our study also found that midazolam combination sedation was associated with the highest sedation success rate but also significantly prolonged LOS ICU. This indicates a potential trade-off between effective sedation and the risk of delirium, which must be considered when developing sedation strategies. Previous clinical studies have also shown that midazolam, compared to propofol or dexmedetomidine, prolongs mechanical ventilation and increases LOS ICU under the same sedation level.[15] Clinically, this may guide the choice of sedative agents, favoring those that minimize the risk of delirium while maintaining adequate sedation levels.

Our study has certain limitations. First, this study is a retrospective observational study. The selection of sedative drugs is affected by the subjective factors of the ICU chief physician; therefore, there is a certain bias. For example, for patients with suspected liver function damage, the chief physician tends to choose single drug sedation strategy and tries to avoid the accumulation effect of midazolam. Secondly, the sample size of this study is small. There are only 24 patients received sedation of propofol combined with dexmedetomidine. Thirdly, the occurrence of delirium is closely related to multiple factors. In this study, all patients were fully conscious and without neurological or psychiatric behavioral abnormalities before surgery. They all underwent total anesthesia surgery with target-controlled infusion (TCI) of combined intravenous and inhalation anesthesia. There were no significant differences in the duration of anesthesia among the three groups. Although there were differences in the time from anesthesia induction to weaning/extubation, these differences were not statistically significant in logistic analysis. This study did not identify any preoperative and intraoperative factors that could affect the occurrence of postoperative delirium in patients. However, more indicators need to be added for further analysis; Fourthly, this study only collected the delirium occurrence of patients during their stay in ICU, and there was no further data record after transferring out of ICU, so it was impossible to trace the incidence of delirium during the entire period of hospitalization. This study may only provide a theoretical basis for the prevention of delirium in ICU for patients after head and neck tumor reconstruction surgery, which still needs to be confirmed by further randomized controlled study; Fifthly, delirium has a variety of clinical manifestations, which can be divided into three types: Hyperactive, Hypoactive, and Mixed Presentation. The hypoactive type is often characterized by patients' apathy, lack of speech, poor reaction and language ability, and less activity,[28] so it is easy to be ignored. This study also did not exclude the possibility of some hypoactive delirium patients being missed.

In conclusion, our study emphasizes the impact of sedation strategies on delirium incidence in patients following head and neck tumor reconstruction surgery. The combined use of midazolam with propofol was identified as a significant risk factor for delirium, emphasizing the need for careful consideration in sedative drug selection. Future studies should aim to address the limitations of this study and further explore the optimal sedation strategies to minimize delirium risk in this vulnerable patient population.

Conclusion

Midazolam combined sedation with propofol showed the highest rate at 28.21% of delirium, significantly higher than the P group at 7.02% and the PD group at 20.83%. Alternative sedation strategies may be necessary to minimize delirium

risk in this vulnerable patient population. Further investigation is warranted through randomized controlled trials to understand the impact of single or combined sedation strategies involving propofol in this patient group.

Ethics Approval and Consent to Participate

This study had passed the exemption of informed consent approved by the Ethics Committee due to its retrospective nature. This study was approved by the Ethics Committee of Nanfang Hospital of Southern Medical University (approval number NFEC-2023-077).

Acknowledgments

We are grateful to Dr. Haihong Fang (Deputy Chief Physician of Department of Anesthesiology, Nanfang Hospital, The First School of Clinical Medicine, Southern Medical University, Guangzhou, China) for his expert review and insightful comments on the sedation protocols used in this study. His input has significantly enhanced the quality and rigor of our research.

Funding

There is no funding to report.

Disclosure

The authors have no competing interests to declare in this work.

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